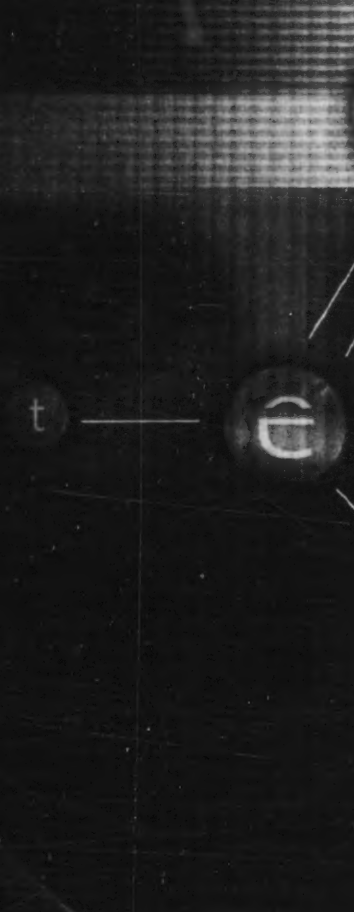
Gamma Knife and Linear Accelerator Stereotactic Radiosurgery



AGENCE D'ÉVALUATION DES TECHNOLOGIES ET DES MODES D'INTERVENTION EN SANTÉ

Québec

Gamma Knife and Linear Accelerator Stereotactic Radiosurgery

Report prepared for AETMIS
by Raouf Hassen-Khodja

French version: October 2002
English version: October 2004

Agence d'évaluation des technologies et des modes d'intervention en santé
Québec

105-06801/

The content of this publication was written and produced by the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS). Both the original report and its French version, titled *La radiochirurgie stéréotaxique par accélérateur linéaire et gamma knife* are available in PDF format on the AETMIS Web site.

Scientific review
Jean-Marie R. Lance, MSc (economics), Senior Scientific Advisor

Proofreading
Frédérique Stephan

Translation
Mark Wickens, Ph.D., Certified Translator

Page layout
Jocelyne Guillot
Frédérique Stephan

Coordination
Lise-Ann Davignon

Communications and dissemination
Richard Lavoie, MA (communications)

For further information about this publication or any other AETMIS activity, please contact:

Agence d'évaluation des technologies et des modes d'intervention en santé
2021, Union Avenue, suite 1050
Montréal (Québec) H3A 2S9

Telephone: (514) 873-2563
Fax: (514) 873-1369
E-mail: aetmis@aetmis.gouv.qc.ca
Web site: www.aetmis.gouv.qc.ca

How to cite this document:

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Gamma Knife and Linear Accelerator Stereotactic Radiosurgery. Report prepared by Raouf Hassen-Khodja. (AETMIS 02-03). Montréal: AETMIS, 2004, xvii-76 p.

Legal deposit
Bibliothèque nationale du Québec, 2004
National Library of Canada, 2004
ISBN 2-550-43208-8 (French edition ISBN 2-55039753-3)

© Gouvernement du Québec, 2004.

This report may be reproduced in whole or in part provided that the source is cited.

MISSION

The mission of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. To accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health care system, in matters concerning the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account many factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

EXECUTIVE

Dr. Luc Deschênes
Cancer Surgeon, President and Chief Executive Officer of AETMIS, Montréal, and Chairman, Conseil médical du Québec, Québec

Dr. Véronique Déry
Public Health Physician, Chief Executive Officer and Scientific Director

Jean-Marie R. Lance
Economist, Senior Scientific Advisor

Dr. Alicia Framarin
Physician, Scientific Advisor

BOARD OF DIRECTORS

Dr. Jeffrey Barkun
Associate Professor, Department of Surgery, Faculty of Medicine, McGill University, and Surgeon, Royal Victoria Hospital (MUHC), Montréal

Dr. Marie-Dominique Beaulieu
Family Physician, Holder of the Dr. Sadok Besrour Chair in Family Medicine, CHUM, and Researcher, Unité de recherche évaluative, Hôpital Notre-Dame (CHUM), Montréal

Dr. Suzanne Claveau
Specialist in microbiology and infectious diseases, Hôtel-Dieu de Québec (CHUQ), Québec

Roger Jacob
Biomedical Engineer, Coordinator, Services des immobilisations, Agence de développement de réseaux locaux de services de santé et de services sociaux de Montréal, Montréal

Denise Leclerc
Pharmacist, Board Member of the Institut universitaire de gériatrie de Montréal, Montréal

Louise Montreuil
Assistant Executive Director, Direction générale de la coordination ministérielle des relations avec le réseau, ministère de la Santé et des Services sociaux, Québec

Dr. Jean-Marie Moutquin
Obstetrician/Gynecologist, Scientific Director, Centre de recherche, CHUS, Sherbrooke

Dr. Réginald Nadeau
Cardiologist, Hôpital du Sacré-Cœur, Montréal, Board Member of the Conseil du médicament du Québec

Guy Rocher
Sociologist, Professor, Département de sociologie, and Researcher, Centre de recherche en droit public, Université de Montréal, Montréal

Lee Soderström
Economist, Professor, Department of Economics, McGill University, Montréal

FOREWORD

GAMMA KNIFE AND LINEAR ACCELERATOR STEREOTACTIC RADIOSURGERY

The huge challenges posed by treating small-volume brain lesions prompted researchers and neurosurgeons to develop a new treatment technique known as "stereotactic radiosurgery" (SRS). Using stereotaxy, which permits the very precise three-dimensional localization of the treatment target, the objective of SRS is to expose the tumor to a single high dose of radiation while at the same time minimizing radiation exposure to the healthy surrounding structures. However, SRS is a leading-edge technology that requires expert skills and the use of elaborate and expensive equipment, such as a linear accelerator or a gamma knife.

The primary objective of this report is to answer the *Régie de l'assurance-maladie du Québec*'s questions concerning the efficacy of SRS in treating brain lesions near sensitive areas. In addition to this objective was the need to determine whether or not it would be beneficial for Québec to acquire a gamma knife. This is why two university hospitals, the regional health and social services boards that these hospitals come under, and the *Ministère de la Santé et des Services sociaux*, which is responsible for the deployment of tertiary services throughout Québec, contacted the *Agence d'évaluation des technologies et des modes d'intervention en santé* to obtain an overview of this issue.

The Agency's assessment is based on a thorough examination of the existing scientific data and an analysis of the epidemiological and economic data applicable to Québec. First, this report briefly explains the underlying principles of SRS and of the different instruments used in this technique. It then examines the efficacy and safety of SRS for various indications. That chapter is followed by a cost comparison of the use of the main instruments utilized in SRS and a discussion of some of the results obtained. Lastly, the Agency draws the appropriate conclusions and makes the appropriate recommendations.

Given the current knowledge about the clinical, economic, technical, and epidemiological aspects, and given the need to adequately fulfill the offer of SRS services and to adequately meet research needs, the Agency recommends that a specialized radiosurgery centre with a gamma knife be set up at a university hospital. The institution chosen must have the necessary logistical wherewithal for SRS, i.e. a multidisciplinary treatment team, patient management quality and continuity, and the role of training. The Agency stresses that this recommendation is conditional upon the technological evolution of the various types of instruments and the emerging therapies at the time when the decision to create a centre providing SRS services is made.

In publishing this report, the Agency wishes to provide the best possible information to the policymakers concerned by this current issue in Québec's health-care system.

Dr. Luc Deschênes
President and Chief Executive Officer

ACKNOWLEDGEMENTS

This report was prepared at the request of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) by **Raouf Hassen-Khodja**, M.D., M.Sc., Consulting Researcher. We wish to express our full gratitude to him for it.

The Agency thanks the following external reviewers for their invaluable comments, which helped improve the quality and contents of this report:

Dr. Jean-Paul Bahary
Radio-oncologist, Chief of Radio-oncology, *Hôpital Notre-Dame, Centre hospitalier universitaire de Montréal*, Montreal, Québec

Dr. Alain de Lotbinière
Neurosurgeon, Director of Stereotactic and Functional Neurosurgery, Department of Neurosurgery, Yale University School of Medicine, New Haven, United States

Dr. Georges L'Espérance
Neurosurgeon, *Clinique médicale René Laennec*, Montreal, Québec, and Director of Professional Care, *Centre hospitalier de Rimouski*, Québec

Dr. Marc Levivier
Professor and Chief of Clinic, Neurosurgery Unit, *Centre Gamma Knife* of *Hôpital Erasme, Université Libre de Bruxelles* (*ULB*), Bruxelles, Belgium

Ervin B. Podgorsak
Director, Physical Medicine Unit, Montreal General Hospital, and Professor, Department of Oncology, Faculty of Medicine, McGill University, Montreal, Québec

Dr. Jean Regis
Hospital Practitioner, Functional Neurosurgery and Gamma Knife Radiosurgery Unit, *Centre hospitalier Régional et Universitaire de Marseille*, France

Lastly, the Agency wishes to thank **Dr. Philippe Couillard**, Neurosurgeon, Chief of Surgery, CHUS, Sherbrooke, Québec; **Dr. André Olivier**, Chief Neurosurgeon, Montreal Neurological Hospital and Institute of the MUHC, and Director and Professor holding the Cone Chair, Neurology Division, McGill University, Montreal, Québec; and **Trudy Brown**, who, when this report was being drafted, was the Director of Strategic Business Services, Elekta Instruments, Norcross, GA, USA, for their assistance and invaluable comments.

CONFLICT OF INTEREST

None declared.

SUMMARY

INTRODUCTION

Thanks to the technological evolution of the different imaging techniques, which are now increasingly precise, the surgical or, more specifically, neurosurgical treatment of certain brain lesions has made tremendous strides. The main advantage of SRS was that it offered greater efficacy while at the same time minimizing the risk. The emergence of approaches using various types of rays (electron, gamma, etc.) and the constant evolution of nuclear physics fostered the development of a new approach in neurosurgery—stereotactic radioneurosurgery. This type of treatment consists in exposing a lesion of small volume, determined by three-dimensional imaging, to a single high dose of ionizing rays while at the same time minimizing the dose absorbed by the surrounding structures.

What is unique about SRS is that it allows one to treat lesions (e.g., the destruction of tumors) without making a surgical incision. With SRS, very delicate and hard-to-reach areas can be treated (e.g., near the optic chiasma) where surgery is not possible because of the risks inherent in the surgical procedures (e.g., hemorrhage, irreversible lesions). The fact that the procedure involves little trauma (local anesthesia) is the other attractive feature of this technique.

The cyclotron, linear accelerator and gamma knife are the three main types of instruments used in SRS. They differ from each other by their radiation source and their mobility in relation to the patient.

In Québec, the use of SRS is limited to the use of the linear accelerator (McGill University Health Centre and *Centre hospitalier universitaire de Montréal*).

BACKGROUND TO THIS ASSESSMENT

In order to be able to process requests for authorizing gamma knife radiosurgery outside Québec, and given the strong likelihood that a request for purchasing this technology will be submitted to the competent authorities, the *Régie de l'assurance-maladie du Québec* asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (Agency) to examine this current issue. Subsequently, two regional health and social services boards, two university hospitals and lastly, the *Ministère de la Santé et des Services sociaux* (given that this issue concerns tertiary care) expressed interest in a more thorough assessment.

In this report, we explain the main principles underlying SRS, discuss the indications for this technique, and present our recommendations concerning the role of SRS in Québec's health-care system.

DESCRIPTION OF SRS

SRS was used for the first time in 1951 by Dr. Lars Leksell. In accordance with the original definition of SRS, its function was to destroy a delimited area of the brain by means of a single dose of radiation and without opening the skull. To this definition, Ladislau Steiner added, in 1997, the notion of "producing desired biological effects".

The basic principle of SRS is the elimination of a functional disorder or the destruction of abnormal tissues by administering a strong dose of highly focussed radiation. This treatment modality enables one to limit the irradiation to the target (small brain lesion) and to spare the healthy surrounding tissues as much as possible. SRS is an important alternative to

the many types of invasive treatment for certain types of brain tumors and enables one to closely monitor the evolution of lesions.

SRS is an external irradiation technique that involves the use of a stereotactic frame and a high-resolution imaging system, such as computed tomography or magnetic resonance imaging. The data gathered are transferred to a digitized-data processing system, which precisely calculates the target's coordinates and characteristics and the radiation doses needed to destroy the lesion by means of an extremely high-performing radiotherapy instrument.

Here are the main types of instruments used in SRS:

- The cyclotron: A circular accelerator of charged heavy particles (e.g., protons and alpha rays).
- The linear accelerator, which can be modified. A modified accelerator can be adapted (by adding stereotactic accessories) or dedicated. It can include a single or multileaf collimator.
- The gamma knife: The patient's head is positioned in the machine by setting its stereotactic coordinates, with the intracranial target located at the isocentre or isocentres. The gamma knife is dedicated solely to SRS.

We excluded the cyclotron from our comparison of the various instruments because it is not mass marketed, is very expensive and requires a very elaborate infrastructure.

EFFICACY OF SRS

Methodology

A literature search was performed in the Medline, Cochrane Library, Embase and HealthStar databases, and was supplemented with reports from a number of health technology assessment agencies that had looked at SRS. Upon examining the relevant scientific data, it was observed that:

- There has been a very large number of study reports on the efficacy of SRS, especially in the past ten years.
- Almost all of the studies have been of the prospective type, with no randomization or comparison.
- Very few or even no comparative studies have examined the use of the gamma knife and linear accelerator (adapted or dedicated) for specific indications.
- Very few economic studies comparing the various instruments have been carried out, and for the most part, they are quoted in the reports published by national assessment agencies.

Results of the analysis

As a general rule, all the results of studies (prospective, retrospective or case studies) support the efficacy of SRS in certain carefully selected cases. The main advantage of this type of treatment over conventional radiotherapy is the improvement in the patient's quality of life.

The indications for SRS that are generally accepted and supported by scientific studies are as follows:

- Arteriovenous malformations.
- Brain metastases. Brain metastases from extracerebral tumors seem to be a target of choice for SRS, especially radioresistant metastases, small tumors, residual or recurrent tumors after surgery, and when one seeks to preserve cranial nerve integrity.
- Meningiomas near sensitive structures.
- Vestibular schwannomas. SRS, especially gamma knife SRS, could be an alternative for overcoming interventional difficulties and avoiding the complications of the standard treatments.

The use of SRS for pituitary adenomas and certain skull base tumors is promising and depends on many different factors, such as the

nature and location of the tumor and the treatment team's experience.

The effects of SRS in patients with functional disorders are not always as convincing as the established benefits of this type of treatment for certain structural brain lesions. The use of SRS will therefore be limited until its efficacy is assessed in rigorous scientific studies.

Because of the lack of comparative data on the clinical efficacy of the gamma knife and the dedicated linear accelerator, it cannot be concluded that either of these instruments is superior to the other. However, the gamma knife does seem to offer the degree of precision required for treating small lesions near sensitive structures, such as the optic chiasma and brainstem, thanks to its technical characteristics. Furthermore, the vast majority of studies have examined the use of the gamma knife for specific pathologies, such as the vestibular schwannoma. This picture could, however, change in light of the technological improvements made to the equipment (especially dedicated linear accelerators), which could increase their precision.

COMPLICATIONS

The adverse effects and complications of SRS can be immediate or late, temporary or permanent, acute or chronic, the healthy adjacent tissues being the main area affected. These effects are usually observed on images of perilesional abnormalities, which depend on various factors, such as the dose administered and the tumor's volume and histological type. The complications range from simple edema to extensive radiation necrosis. Depending on the location and type of lesion, these complications manifest clinically as transient headaches or a specific symptomatology associated with the location of the necrosis.

A good knowledge of the probability of adverse effects occurring, rigorous dose planning and a longer follow-up for certain pathologies can limit the adverse effects and complications.

SAFETY AND PREVENTIVE MEASURES

Like any other treatment that uses radiation sources, SRS requires the preventive measures inherent in radiotherapy. Setting up an SRS unit involves applying and maintaining the necessary radiation protection standards (structures, patients and personnel) and establishing control measures—in some cases, specific—for certain instruments. While the preparation and adjustment protocol may be uniform for the gamma knife, it is not so for linear accelerators, especially those that are not neurosurgery-dedicated. As a general rule, there are four control steps: adjusting the machine, preparing the patient, locating the target and transferring the data, and lastly, determining the ballistics and dosimetry.

For these measures, each treatment team member must have specific skills and qualifications. Patient management depends on several factors, including the technical/medical team's multidisciplinary makeup. Apart from the personnel normally present during radiotherapy, a neurosurgeon and a neuroradiologist should participate in the treatment.

CURRENT AND POTENTIAL NEEDS IN QUÉBEC

The results of the various prospective studies all indicate that the number of patients who will eventually require SRS is about at least 40 per one million population per year. In Québec, this would work out to about 300 cases a year (1,200 for all of Canada). This calculation concerns only three indications (metastases, schwannomas and vascular malformations). Other authors arrive at much higher figures in the order of 180 cases per one million population per year (or 1,260 in Québec). In our opinion, and based on data from the *Fichier des tumeurs du Québec* and from Canadian Cancer Statistics 2000, a more

cautious calculation brings the number of eligible cases in Québec to 400. More specifically, and based on existing epidemiological data, we estimate the number of cases of arteriovenous malformations to be between 100 and 120 per year, while the number of cases of brain metastases potentially eligible for SRS would be between 400 and 1,200 per year.

THE COST OF SRS

In a first approximation, if the comparison involves the same number of treated patients, each gamma knife treatment would cost slightly less than if a dedicated linear accelerator were used (assuming that the instruments' lifespans are 20 and 10 years, respectively) and would be more expensive than treatment by means of an adapted linear accelerator. If the use of an adapted linear accelerator is shared between radiotherapy and radiosurgery, the number of cases that could be treated by radiosurgery at each facility would reach a ceiling.

The number of patients treated is an important variable in determining the average cost per treatment, since this cost (excluding physicians' fees) can drop from $11,000 to $4,500 CAD as the number of treatments performed with the gamma knife and dedicated linear accelerator increases from 100 to 250. However, the optimal treatment capacity depends on the amount of time it takes to reach this capacity and the number of truly eligible cases in the population.

Based on an evaluation carried out in Québec, the purchase and renovation costs for a gamma knife are approximately $6.44 million. A dedicated linear accelerator would cost about one half this amount, but its operating costs (physical and human resources) would be 50% higher. It follows that the total cost, including amortization of the instruments, the radiation sources and the renovations, are approximately the same. As for the adapted linear accelerator, its total cost is 15 to 30% less than that of the gamma knife, given an annual treatment volume of between 175 and 100. All of these figures are based on the purchase of new instruments.

It is difficult to perform a cost-effectiveness analysis because of the lack of randomized studies comparing the various instruments with respect to their clinical efficacy and because the cost of treatment often depends on the patient's clinical status and on the type of treatment considered (first-line treatment, treatment of recurrences, adjuvant SRS).

In the end, if it is assumed that the treatment is of equal efficacy regardless of the instrument used, the economic comparison criterion would be limited to the per-treatment cost. However, the evaluations do not show a significant difference between the dedicated linear accelerator and the gamma knife, which are more comparable from the standpoint of clinical performance. Lastly, the number of cases that are truly eligible and actually treated is a crucial factor.

CONCLUSIONS

Stereotactic radiosurgery

- The efficacy of SRS has been established for a certain number of indications, including brain metastases, arteriovenous malformations, as an alternative to conventional surgery in cases of interventional difficulties, and in the avoidance of the complications of the standard treatments in cases of meningioma and vestibular schwannoma. SRS is a promising approach in the treatment of pituitary adenomas, certain skull base tumors, and specific functional disorders.

- Given the evolution of the technologies and the costs associated with SRS, the instruments that might best meet the efficacy and safety criteria are the dedicated linear accelerator and the gamma knife.

- The use of an adapted linear accelerator is possible but limited in cases of lesions in very close proximity to sensitive structures, since the manipulations required to

adapt the equipment in order to perform SRS can be a source of imprecision when focussing the beams. Furthermore, the need to perform quality control before each treatment lengthens the treatment time.

- Presently, SRS facilities are clearly needed in Québec. If we consider all the lesions eligible for SRS on the basis of the existing data and evaluations, more than 300 patients could qualify for SRS.

Therapeutic efficacy by instrument

- Even if, in theory, the gamma knife and dedicated linear accelerator are both more suitable for the different indications for SRS, technological developments in the specific area of SRS (especially in the case of the dedicated linear accelerator) and the lack of randomized, controlled trials concerning a given indication do not permit us to conclude that either of these instruments is superior to the other from the standpoint of efficacy. However, the degree of precision offered by the gamma knife permits the treatment of lesions that are no more than 2 mm in size and which touch vital structures, such as the cranial nerves, optic chiasma and brainstem, without (theoretically) causing any injury to healthy tissues.

SRS in the Québec context

- Given the current knowledge about the clinical, economic, technical and epidemiological aspects, and given the need to adequately fulfill the offer of SRS services and to adequately meet research needs, the Agency recommends that a specialized radiosurgery centre with a gamma knife be created at a university hospital. Where this specialized centre will be set up will depend on geographical and/or functional accessibility and well-established service pathways.

- The institution chosen must have the necessary logistics (structural and professional) needed to perform this type of treatment. The mandatory presence of a multidisciplinary team (neurosurgeon, neuroradiologist, radiation therapist, radiophysicist, paramedical personnel), the need to provide continuous patient management quality and the need to promote the acquisition of new professional skills clearly warrant creating the centre at a university hospital.

- These conclusions are conditional upon the technological evolution of the various types of instruments and the emerging therapies (fractionated stereotactic radiotherapy) at the time when the decision to create a centre providing SRS services is made.

GLOSSARY

Angioma
A malformational (dysgenetic angioma) or acquired (neoplastic angioma) vascular tumor of the cells that line blood (hemangioma) or lymph (lymphangioma) capillaries.

Astrocytoma
A benign glial tumor whose malignant transformation is very frequent in certain parts of the central nervous system.

Bragg's peak
The distribution of the radiation dose along the protons' trajectory (proton therapy). The dose delivered increases as the particles' energy decreases.

Brain metastasis
The occurrence, in the brain, of cancer cells that have spread from a distant primary tumor outside the brain.

Craniopharyngioma
A suprasellar pituitary tumor arising from Rathke's pouch. It is sometimes cystic and lined with a malpighian epithelium.

Cyclotron
A circular heavy-particle accelerator that uses a fixed magnetic field and an electric field of constant frequency.

Ependymoma
A tumor of the glioma group that arises from ependymal cells during the first two decades of life. It usually occurs in the posterior fossa and spinal cord and generally has a benign prognosis.

External radiotherapy
The therapeutic use of x-rays emitted by an external source (roentgenotherapy).

Fractionated
Refers to radiotherapy administered in doses spread out over several sessions. In stereotactic radiosurgery, treatment is administered in a single dose.

Gamma knife
Leksell Gamma Knife® is a registered trademark of stereotactic radiosurgery equipment using cobalt-60 sources.

Glial
Relating to the neuroglia.

Glioblastoma
A malignant brain tumor composed of a proliferation of undifferentiated glial cells.

Glioma
Any tumor that has developed from the adult or embryonic neuroglia. Includes all primary tumors of the brain and spinal cord (astrocytoma, ependymoma, neurocytoma).

Hamartoma
A benign pseudotumor characterized by an excessive quantity or abnormal arrangement, in a tissue or an organ, of cells that normally occur there.

Hemangioblastoma
A type of hemangioma (vascular tumor) specific to the nervous system. It usually occurs in the posterior cranial fossa and is characterized by the presence of nerve tissue between the vascular bundles (cerebellum, spinal cord, etc.). Called also *angioblastoma*.

Hemangioma
A true angioma, composed of newly formed, dilated vessels.

Isocentre
A point located at the intersection of the central axis of a beam and the axis of the rotating or arced movement of the x-ray tube.

Karnofsky's index
A score, expressed as a percentage, defining a patient's clinical and functional status (commonly used in terminally ill patients).

Linear accelerator (or **linac**)
An instrument that emits electrons of very high kinetic energy by means of an electric field. It is said to be adapted (or modified) when accessories are added for the purpose of using the instrument in stereotactic radiosurgery or dedicated when it is manufactured to be used exclusively in stereotactic radiosurgery.

Medulloblastoma
A radiosensitive tumor that usually occurs in children, most often in the vermis.

Meninges
The set of three membranes that completely envelop the brain and spinal cord. They are, from the outside in, the dura mater (pachymeninx), arachnoid and pia mater, the latter two being, respectively, the parietal and visceral layers of the leptomeninges and between which cerebrospinal fluid flows.

Meningioma
A benign intracranial or intraspinal tumor arising from the meninges.

Multileaf collimator
A collimator in which the position of each leaf is calculated by computer. Each leaf is used to precisely guide a beam of rays to the lesion and to prevent irradiation of the healthy, adjacent tissues. There are many different models of linear accelerators with multileaf collimators.

Neurinoma
A benign tumor arising from the sheath of Schwann of the peripheral nerves or spinal roots, usually occurring on the auditory nerve. Called also *schwannoma*.

Neuroglia
The supporting tissue of the nervous system. It consists of a network of highly branched cells (glial or neuroglia cells). Called also *glia*.

Percentage depth dose
The ratio, expressed as a percentage, of the dose absorbed at a given depth in the body to the dose absorbed at a reference point on the axis of radiation.

Pituitary adenoma
A benign tumor of the pituitary gland; it is implicated in many different conditions, such as acromegaly and Cushing's syndrome.

Pituitary tumors
Tumors of the pituitary gland, including secreting pituitary adenomas and craniopharyngiomas.

Relative biological efficacy
A factor used by some authors to compare various types of radiotherapy.

Schwannoma
See *neurinoma*.

Stereotactic radiosurgery
A treatment technique developed by Leksell in which the brain is irradiated with tiny beams under stereotactic conditions and which involves exposing a lesion of small volume, determined by three-dimensional imaging, to a single high dose of ionizing rays.

Stereotactic radiotherapy
A type of fractionated radiotherapy performed under stereotactic conditions using a frame whose position can be changed.

LIST OF ABBREVIATIONS

AETS	*Agencia de evaluación de technologías sanitarias* (Health Technology Assessment Agency), Madrid, Spain
AHFMR	Alberta Heritage Foundation for Medical Research, Alberta
ANAES	*Agence nationale d'accréditation et d'évaluation en santé*, France
AVM	Arteriovascular malformation
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CEDIT	*Comité d'Évaluation et de Diffusion des Innovations Technologiques* (*Assistance publique, Hôpitaux de Paris*, France).
CHUS	*Centre hospitalier universitaire de Sherbrooke*
CT	Computed tomography
DM	*Deutsche mark*
ICD	International Classification of Diseases
GK	Gamma knife
Gy	Gray
MRI	Magnetic resonance imaging
MSAC	Medicare Services Advisory Committee, Australia
OHRC	Oregon Health Resources Commission, USA
RTOG	Radiation Therapy Oncology Group, USA
SRS	Stereotactic radiosurgery
VS	Vestibular schwannoma

TABLE OF CONTENTS

MISSION iii
FOREWORD v
ACKNOWLEDGEMENTS vi
SUMMARY vii
GLOSSARY xii
LIST OF ABBREVIATIONS xv

1 INTRODUCTION 1
2 METHODOLOGY 2
3 DESCRIPTION OF RADIOSURGERY 3
3.1 General principes 3
3.2 Types of instruments used 4
3.2.1 Single fixed source and moving patient: the cyclotron 4
3.2.2 Single moving source and moving patient: the linear accelerator 5
3.2.3 Fixed source and stationary patient: the gamma knife 6
4 INDICATIONS 9
4.1 Vascular lesions 9
4.2 Brain tumors 12
4.2.1 Brain metastases 12
4.2.2 Pituitary tumors 16
4.2.3 Meningiomas 19
4.2.4 Vestibular schwannomas 22
4.2.5 Gliomas 24
4.3 Trigeminal neuralgia 25
4.4 Other PATHOLOGIES 27
4.4.1 Other tumors 27
4.4.2 Parkinson's disease 27
4.4.3 Epilepsy 27
4.4.4 Obsessive-compulsive disorders 28
4.5 Summary of the efficacy of SRS 29
5 COMPLICATIONS 30
6 SAFETY AND PREVENTIVE MEASURES 33
7 CURRENT DATA AND INCIDENCE OF TARGET PATHOLOGIES IN QUÉBEC 35
8 COST OF SRS 36
8.1 Cost of SRS by instrument 36
8.2 Comparison between SRS and neurosurgery 39
8.3 cost-effectiveness 40
8.4 Conclusion 41
9 DISCUSSION 43
10 CONCLUSION 45
APPENDIX A: TECHNICAL CHARACTERISTICS OF VARIOUS SRS INSTRUMENTS 47
APPENDIX B: MAIN DIFFERENCES BETWEEN SRS INSTRUMENTS 48
APPENDIX C : PROTON THERAPY 49
APPENDIX D: THE LINEAR ACCELERATOR 50
APPENDIX E: THE GAMMA KNIFE 51

APPENDIX F: STATUTES AND REGULATIONS CONCERNING RADIOSURGERY 52
APPENDIX G: FACTUAL INFORMATION 54
APPENDIX H: SRS INSTRUMENT COST DATA 57
REFERENCES 60

LIST OF FIGURES AND TABLES

Figure C.1 Proton therapy unit 49
Figure C.2 Diagram of Bragg's peak 49
Figure D.1 Diagram of one type of linear accelerator (both source and patient move) 50
Figure D.2 Linear accelerator with integrated, 3-dimensional multileaf collimator (PRIMUS linear®) 50
Figure E.1 Drawing of a gamma knife and a patient during treatment 51

Table 1 Results of studies examining various types of SRS treatment for vascular lesions 11
Table 2 Results of studies examining SRS for brain metastases 13
Table 3 Results of studies of SRS for pituitary tumors 17
Table 4 Results of studies of SRS for meningiomas 21
Table 5 Results of studies of SRS for vestibular schwannomas 23
Table 6 Results of studies of SRS for gliomas 25
Table 7 Results of studies of SRS for trigeminal neuralgia 26
Table 8 Number of brain tumors, both sexes combined, Québec, 1992-1996 35
Table 9 Acquisition and annual operating costs for SRS instruments 37
Table 10 Total per-patient cost of traitement by instrument 38
Table 11 Comparison between SRS and microsurgery 40
Table 12 Cost estimates (in US dollars) by type of procedure 41
Table G.1A Overall incidence of brain metastases by type of primary cancer 54
Table G.1B Estimated number of brain metastases per year by location of the primary tumor 54
Table G.2 Karnofsky's index 55
Table G.3 Number of brain tumors diagnosed in Québec (1992 to 1996) 55
Table G.4 Potential indications for SRS 56
Table G.5 Indications for SRS and estimate of the number of eligible candidates in québec 56
Table H.1 Cost of instrument per patient (in Canadian dollars) 57
Table H.2 Total cost per patient and per treatment 57
Table H.3 Acquisition, renovation and maintenance costs for a gamma knife 58
Table H.4 Total per-patient cost (in Canadian dollars) of treatment by gamma knife according to the CHUS study 59
Table H.5 Total per-patient cost of treatment (Elekta® study) in constant canadian dollars 59

1 INTRODUCTION

Technologically, radiotherapy has evolved considerably over the past few decades. This has led to the emergence of new specialties that differ from radiotherapy by the applied technologies, the treatment modalities and the therapeutic effects. Stereotactic radiosurgery (SRS) is one of the main applications that has resulted from these technological advances (technique designed exclusively for neurosurgical purposes). It involves exposing a lesion of small volume, which is determined by three-dimensional imaging, to a high dose of ionizing rays whose precise targeting minimizes irradiation of the surrounding structures.

The linear accelerator is currently the only instrument used in Canada for SRS, although a first acquisition project has been approved in Winnipeg, Manitoba. The growing number of patients and the variety of tumors are prompting health professionals to acquire the highest-performing technological tools and to use the most effective and appropriate approaches to treating the conditions in question. One of the instruments used in SRS, the gamma knife, differs by its intended purpose, for unlike the linear accelerator, which needs to be modified or to which certain accessories need to be added for use in SRS, the gamma knife is dedicated solely to SRS.

What is unique about SRS is that it allows one to treat lesions (e.g., destroying tumors) without making a surgical incision. With SRS, very delicate and hard-to-reach areas can be treated (e.g., near the optic chiasma) where surgery is not possible because of the inherent risks (e.g., hemorrhage, irreversible lesions). The fact that the procedure involves little trauma (local anesthesia) is the other attractive feature of this technique.

In order to be able to process requests for authorizing gamma knife radiosurgery outside Québec, and given the strong likelihood that a request for purchasing this technology will be submitted to the competent authorities, the *Régie de l'assurance-maladie du Québec* asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (Agency) to examine this current issue. Subsequently, two regional health and social services boards (Montreal-Centre and Estrie) and two university hospitals (the McGill University Health Centre and the *Centre hospitalier universitaire de Sherbrooke* [CHUS]) contacted the Agency directly to express their interest in a more thorough assessment. Lastly, the *Ministère de la Santé et des Services sociaux* got involved in the process as well, given that this matter concerns tertiary care.

This report explains the main princip s underlying SRS, discusses the indications for this technique, and contains our recommendations concerning the role of SRS in Québec's health-care system.

2 METHODOLOGY

A literature search was performed in the Medline, Cochrane Library, Embase and HealthStar databases. The keywords used were *radiosurgery*, *stereotactic radiosurgery*, *radiotherapy*, *linac*, *accélérateur linéaire*, *gamma knife*, and *protontherapy*. These keywords were crossed with the terms *costs*, *cost analysis* and *cost-effectiveness* so that the economic aspects could be examined. The search covered all articles and study reports dealing with SRS published up to the present time.

Other, unindexed reports were taken into consideration, in particular, that of the *Comité d'Évaluation et de Diffusion des Innovations Technologiques* (CEDIT), which is affiliated with *Assistance Publique, Hôpitaux de Paris*, France, [Courtay, 1998] and that of CHUS [2000].

Here are a few observations worthy of mention:

- Even if the results of the studies of fractionated stereotactic radiotherapy are encouraging, this new technology (came into being four years ago) will not be covered in our report, since it does not fit the general definition of SRS. SRS involves the administration of a single dose of radiation, whereas fractionated stereotactic radiotherapy involves the administration of low doses spread out over several sessions. Furthermore, tumors treated with fractionated stereotactic radiotherapy are usually larger.
- There has been a very large number of study reports on the efficacy of SRS, especially in the past ten years.
- Almost all of the studies have been of the prospective type, with no randomization or comparison.
- Very few or even no comparative studies have examined the use of the gamma knife and linear accelerator (adapted or dedicated) for specific indications.
- Very few economic studies comparing the various instruments have been carried out, and for the most part, they are quoted in the reports published by national assessment agencies, such as the *Agence nationale d'accréditation et d'évaluation en Santé* (ANAES) in France [ANAES, 2000]; the Alberta Heritage Foundation for Medical Research (AHFMR) [Schneider and Hailey, 1998]; the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) [CCOHTA, 1992]; and the Medicare Services Advisory Committee (MSAC) in Australia [MSAC, 2001].

Given the paucity of comparative studies of the various instruments used in SRS, we included in the analysis those that met certain criteria regarding the type of indication, the study methodology and the number of participants, in order to prepare an exhaustive account of the differences observed among the authors' conclusions.

3 DESCRIPTION OF RADIOSURGERY

Thanks to the technological evolution of the different imaging techniques, which are now increasingly precise, the surgical or, more specifically, neurosurgical treatment of certain brain lesions has made tremendous strides. These lesions are characteristically located in areas of the brain that are often very hard to reach or very close to delicate or vital structures. The main advantage of SRS is that it offers greater efficacy while at the same time minimizing the risk. This advantage played a decisive role in the search for new treatment techniques for the central nervous system (CNS). The emergence of approaches using various types of rays (electron, gamma, etc.) and the constant evolution of nuclear physics fostered the development of a new approach in neurosurgery—stereotactic radioneurosurgery.

The concept of SRS was used for the first time in 1951 by Dr. Lars Leksell [Leksell, 1951]. "Stereotactic radiosurgery" referred to the exposure of small brain lesions to a single high dose of radiation. To this, Leksell's original definition, where the function of SRS was to destroy a delimited area of the brain with a single high dose of radiation without opening the skull, Ladislau Steiner added the notion of "producing desired biological effects" [Prasad, 1999; Steiner et al., 1997].

Although this concept came into being less than a half century ago, it has evolved quickly, thanks to the discovery of new applications and to rigorous scientific studies that have made it possible to determine the indications for SRS and the clinical approaches and to ensure its technological development.

3.1 GENERAL PRINCIPES

The basic principle of SRS is the elimination of a functional disorder or the destruction of abnormal tissues by administering a strong and highly focused dose of radiation. This treatment modality enables one to limit the irradiation to the target (small brain lesion) and to spare the healthy, surrounding tissues as much as possible [Davey, 1999].

Stereotactic neurosurgery is an external irradiation technique that involves the use of a stereotactic frame and a high-resolution imaging system, such as computed tomography (CT) or magnetic resonance imaging (MRI). The data gathered are transferred to a digitized-data processing system, which precisely calculates the target's coordinates and characteristics and the radiation doses needed to destroy the lesion by means of an extremely high-performing radiotherapy instrument.

The main types of instruments used in SRS differ according to the radiation source and the instrument's mobility in relation to the patient. The main instruments used are as follows:

- The cyclotron, a circular accelerator of charged heavy particles (e.g., protons and alpha rays).
- The linear accelerator [Colombo and Francescon, 1998], which can be modified [Hakim et al., 1998; Friedman and Bova, 1989]. A modified accelerator can be adapted (by adding stereotactic accessories) or dedicated. It can include a single or multileaf collimator (e.g., the Peacock® system).
- The gamma knife: The patient's head is positioned in the instrument by setting its stereotactic coordinates, with the intracranial target located at the isocentre or isocentres.

Additional information is provided in Appendices A and B if the reader wishes to make a rapid comparison of these instruments and their respective advantages and limitations.

From a technical standpoint, SRS is an important alternative to the many invasive forms of treatment for certain types of brain tumors [Alexander and Loeffler, 1999; Loeffler and Lindquist, 1999]. Together with data obtained by CT or MRI, the stereotactic frame is used to precisely locate the tumor and to closely monitor its evolution. As we shall see in this report, the use of SRS depends on many different factors, including:

- Tumor volume
- Tumor shape
- Tumor invasiveness
- Tumor location
- Tumor histology
- The patient's clinical status

The precision of the treatment depends on the image of the lesion, the technique used to acquire the image and the incorporation of this image into the treatment procedure.

The principles underlying radiobiology apply to SRS as well. The biological consequences of SRS are the irreversible destruction of tissues and the late occurrence of vascular occlusions. All tissues (abnormal and healthy) in the target are destroyed [Foote et al., 1999]. For some indications, the irreversible destruction of tissue is not a condition for therapeutic efficacy [Grant and Woo, 1999; Harsh et al., 1999].

3.2 TYPES OF INSTRUMENTS USED

3.2.1 Single fixed source and moving patient: the cyclotron

Proton therapy is a type of high-precision radiotherapy based on the emission of heavy, positively charged particles, protons. Technological advances, in particular those in three-dimensional dosimetry and digital imaging systems (CT and MRI), have led to the more widespread use of proton therapy. Because of the very elaborate infrastructure that proton therapy requires (as can be seen from the diagram of a proton therapy instrument in Appendix C) and because of its extremely high cost, the use of this modality is limited to exceptional cases, despite the fact that more than 20,000 patients worldwide have been treated with it since its inception.

Proton therapy can be used to treat any radiosensitive tumor (nonmetastatic), such as brain and skull base tumors, especially those near sensitive or vital organs (functional structures).

Currently, there are 11 proton therapy facilities in Europe, including two in France and three in Russia, five in North America, one of which is in Canada (British Columbia), two in Japan and lastly, one in South Africa.

Technical characteristics

A cyclotron combines an axial magnetic field produced by magnets and a high-frequency, radial, alternating electrical field between two semicircular structures called "dees". The proton beam is obtained by ionizing hydrogen particles and accelerating the protons with the magnetic field produced by the cyclotron. Once the desired energy is achieved, the protons are modulated and emitted as rays.

Several different models of cyclotron are used in SRS. As a general rule, a circular metal frame is attached to the patient's head (with local anesthesia). The instrument is stationary, and the patient rotates around a precise target point.

In the case of protons, the administered radiation dose decreases with the square of the distance between the target and radiation source.

Mechanism of action

The principle of proton therapy is based on the properties of protons, which derive from their electrical charge and mass (1,836 times greater than that of electrons). These properties are as follows: little lateral diffusion, a precise trajectory, which depends on the

protons' energy (precision down to 0.1 mm), and maximum energy released at the end of the trajectory (target), or at Bragg's peak (Figure 2, Appendix C). Since the irradiation is better focused, injury to the tissues that the protons pass through is minimized [Kitchen, 1995; Lindquist et al., 1991].

The biological effects of proton therapy are quantitatively and qualitatively comparable to those of conventional radiotherapy (relative biological efficacy from 1.0 to 1.25).

Treatment procedure

The procedure consists of the following four steps:

1. Localization of the lesion by CT. This is an important step, since the images are used to determine the location of the various structures with a high degree of precision (targets, adjacent structures).
2. Planning of the treatment and determination of the beam axis in order to optimize the effectiveness of the treatment.
3. Preparation of a custom-made restraining helmet for immobilizing the patient's head for the entire duration of the treatment.
4. Treatment: About 10 short sessions (positioning the patient takes longer) are generally necessary.

In our cost comparison of the instruments used in SRS, we excluded the cyclotron (cyclotrons are not mass-marketed). The acquisition and renovation costs (approximately $12 million) and the physical operating conditions make this technology unaffordable in the context of this assessment.

3.2.2 Single moving source and moving patient: the linear accelerator

In this technology, both the patient and the source move (Figure 1, Appendix D). As a result, a larger number of targets can be irradiated [Podgorsak et al., 1988; Karzmark, 1984]. The linear particle accelerator therefore emits X photons within the context of dynamic radiotherapy. Two types of linear accelerators are used in SRS, the adapted or modified accelerator (special accessories added for shared use between conventional radiotherapy and SRS) and the dedicated accelerator (reserved exclusively for SRS). There are many different models of linear accelerators, the latest of which are equipped with integrated, three-dimensional multileaf collimators (Figure 2, Appendix D).

Technical characteristics

The linear accelerator is used in arc therapy, that is, to emit a high-energy beam (of adjustable diameter) that travels in the shape of an arc, its centre of movement being the centre of the target lesion volume, hence the notion of isocentre. The mechanical movements thus produced are responsible for the inaccuracies in spatial dosimetry, which is very complex. The energy released by a linear accelerator varies according to the instrument and ranges from 4 to 18 million electron volts (MeV). The first linear accelerators offered precision of about 0.3 mm, which precluded their use in the treatment of lesions of the brain stem, optic chiasma and ventricles, for fear of injuring the healthy tissues in these structures. According to some manufacturers, the modifications made since then enable one to achieve precision of 0.2 mm. However, Meeks et al. indicate that study reports concerning the modification of linear accelerators show highly mixed results [Meeks et al., 1999].

Certain types of linear accelerators are equipped with multileaf collimators, which make it possible to guide the beam to the target with greater precision while at the same time preventing rays from reaching the healthy, adjacent tissues. The clinical evaluation of such instruments, which began to be used fairly recently, continues.

Mechanism of action

Like conventional radiotherapy, linear accelerator photon radiosurgery destroys cells, arrests tumor growth or both. In addition, it is

credited with playing a role in the gradual obliteration of small-caliber vessels.

Treatment procedure

SRS is considered a surgical procedure in which the neurosurgeon is responsible not only for attaching the stereotactic frame, but also for determining the anatomical location of the target structures. Generally, the patient is followed on an outpatient basis and is premedicated on the day of the procedure. When performed with a dedicated linear accelerator, SRS consists of the following steps:

1. The stereotactic frame is attached to the patient's head (with four small screws) using local anesthesia. This takes about 20 minutes.
2. The target or targets are localized by MRI or CT.
3. The images are transferred via a network to the dosimetry calculation system (treatment plan).
4. The volume of each target is delimited. The circumscribed target volume can also be displayed in three dimensions.
5. The treatment ballistics are determined. The patient undergoes noncoplanar arc therapy sessions (generally four to six, with table rotation), which focus on the centre of each target. The isodose envelope is determined. It is 70% of the dose delivered to the centre of each target and completely encloses the target volume.
6. The treatment is planned by a multidisciplinary team (oncologist, physicist and neurosurgeon). This complex step often takes a great deal of time. The go-ahead to start the treatment is given jointly by the physicist and the oncologist. The linear accelerator rotates several times around the patient's head.
7. Once the treatment is completed, the stereotactic frame is removed, and, in some cases, the points of attachment are treated locally.

If an adapted linear accelerator is used, a few additional steps will be necessary when preparing the equipment, such as adding stereotactic accessories and recalibrating the instrument. These manipulations can cause precision problems and therefore require repeated and rigorous quality control [Meeks et al., 1999].

Treatment by means of a linear accelerator can vary somewhat with the instrument used and is closely tied to the use of dosimetry software and image processing systems, features that can differ according to the manufacturer.

3.2.3 Fixed source and stationary patient: the gamma knife

Technical characteristics

The main improvements made to the gamma knife are essentially aimed at incorporating a computerized dosimetry system, which, in those of its applications where it performs best, enables the team to plan the administered dose in real time and in three dimensions. The gamma knife is an instrument dedicated almost exclusively to interventions involving brain structures or structures contiguous to the brain. It is of optimal utility for certain brain abnormalities and tumors, and for a few disorders of cerebral origin. The use of the gamma knife involves attaching a stereotactic frame on the patient's head and the emission of rays from a fixed source (Appendix E).

The main distinguishing feature of the gamma knife is its high number of radiation sources. It uses 201 fixed cobalt-60 sources distributed evenly over a hemispheric device, each emitting a fine beam of rays. The patient's head is positioned in such a manner that only the lesions at the target focus are treated. This configuration makes it possible to focus all the beams onto a common target [Leksell, 1971a; Leksell, 1951]. The diameter of the beams and the arrangement of the sources make it possible to optimize the intensity of the radiation directed at the target (effective biological dose) while at the same time minimizing irradiation of the healthy, adjacent tissues. The

gamma knife can be used to treat lesions measuring no more than 2 mm that are touching vital structures, such as the cranial nerves, optic chiasma and brain stem, without injuring (theoretically) healthy tissues.

The numerous study reports concerning the gamma knife discuss the advantages that this technology can offer, such as:

- The possibility of using small-diameter beams (4 to 8 mm) with a targetting precision in the order of 0.3 mm (with mechanical collimation). However, the overall precision also depends on the stereotactic frame and its positioning, and on the imaging process. Ertl et al. achieved overall precision of within a fraction of a millimetre (0.72 ± 0.20 mm in the direction of the temporal bone) in an experimental study of the radiation emitted by a gamma knife (model B) [Ertl et al., 1999]).
- The possibility of incorporating a high-resolution imaging system that facilitates SRS.
- The ability to irradiate many isocentres easily without injuring adjacent vital structures.
- The production of experimental models in radiobiology.
- The use of a standard technique employed at many centres throughout the world for gathering data and developing multicentre studies.

The use of the gamma knife and of its Chinese equivalent, the Rotating Gamma System, is based on the same technical procedures and the same radiation source: multisource targeting and selective irradiation adapted to the shape and volume of the tumor or lesion. This type of instrument enables one to maximize the radiation doses, to expose the surface to be treated to rays of uniform intensity and to minimize injury to healthy tissue. The Model C gamma knife, which is currently being evaluated, is equipped with an automatic positioning system whereby the patient's head can be positioned automatically according to the target's three-dimensional coordinates, which are obtained by means of a scanner.

Mechanism of action

Theoretically, and depending on the nature of the pathology, the rays emitted by a gamma knife produce the following effects:

- The destruction of tumor cell DNA, thus halting cell replication and proliferation and causing cell death.
- The proliferation of endothelium, which leads to the occlusion of these malformed vessels (endarteritis obliterans) and therefore to the destruction of structural abnormalities (e.g., arteriovenous malformations).
- In certain pathologies, the obtaining of a brain cell lesion causing decreased neurotransmitter secretion (e.g., thalamotomy, pallidotomy in certain dyskinesias).
- The eventual reduction or even elimination of the excess nerve impulses responsible for pain syndromes (e.g., trigeminal neuralgia) through the use of low doses.

Treatment procedure

Gamma knife SRS involves the following five steps:

1. Attaching a stereotactic frame. After administering a mild sedative to the patient, the frame is attached to his/her head with four screws. This step, which is performed with local anesthesia, takes five minutes.
2. Digital imaging. A type of MRI is used to determine the position of the target in relation to the stereotactic frame. CT is used when MRI is not possible (pacemaker, etc.).

3. Developing a treatment plan from the digitized image of the lesion.

4. Placing the patient on the table. Headphones are made available to the patient. The required dose is administered over a period of 30 or more minutes, depending on the complexity of the treatment and the sources' radioactivity (it decreases with time).

5. Removing the stereotactic frame and applying bandages (generally two hours), after which the patient is observed for a few hours, then discharged the same day.

4 INDICATIONS

The main indications for SRS are tumoral lesions in general and neurological lesions in particular. SRS is occasionally used for other conditions as well, but the results are only more or less encouraging and have not been published in reports from any randomized, comparative clinical studies. For certain mental disorders, such as obsessive-compulsive disorders and epilepsy, the use of SRS is still much debated. Currently, the many study reports concerning these disorders present mixed results. These studies compared SRS and standard treatment techniques (e.g., thermosurgery) or, more rarely, different SRS instruments, with other studies limited to presenting case reports on novel approaches using radiosurgery for conditions that are refractory to the standard treatments.

The main conditions of interest in these studies are as follows:

Vascular lesions

- Arteriovenous malformations
- Cerebral cavernomas

Intracranial tumors

- Brain metastases
- Primary tumors
  - Pituitary adenomas
  - Meningiomas
  - Auditory nerve neurinomas
  - Neurinomas (trigeminal schwannomas)
  - Glial tumors
  - Hemangioblastomas
  - Glomus tumors
  - Pineal tumors
  - Craniopharyngiomas (extracerebral)
  - Chordomas (extracerebral)
  - Chondrosarcomas (extracerebral)
  - Ocular melanomas

Other functional disorders and refractory pain

- Trigeminal neuralgia
- Parkinson's disease
- Epilepsy
- Certain psychoneuroses
  - Obsessive-compulsive disorders

4.1 VASCULAR LESIONS

Thanks to MRI, vascular malformations undetected by cerebral angiography can be visualized [Kida et al., 1999]. This group of lesions includes various entities, such as cavernous malformations, thrombosed arteriovenous malformations (AVMs), and telangiectasias. These lesions often occur in particularly sensitive areas, such as the brain stem and the hypothalamus.

It should be noted that the validity of the studies is low, since there have been no comparative studies, but rather prospective (cohort follow-up), retrospective or case series studies. Table 1 summarizes the results of the studies examined.

Most of the study reports concerning SRS for cerebral AVMs discuss the efficacy of this technique when used alone or as an adjuvant to surgical resection [Chang et al., 1998c], endovascular embolization [Paulsen et al., 1999a; Paulsen et al., 1999b] or more complete treatment combining embolization and resection. The smaller the AVM, the greater the efficacy of SRS (by linear accelerator or gamma knife) [Debus et al., 1999].

The treatment of choice for lesions outside the above-mentioned structures and for epileptic foci is surgical excision. However, SRS is very useful in the other situations and reduces the occurrence of hemorrhage considerably [Alexander et al., 1995]. No neuropsychological

effects on the patients are mentioned in the preliminary results of the study conducted by Blonder et al. involving 10 patients with AVMs [Blonder et al., 1999].

Even if the use of SRS for AVMs is widespread, the optimal dose-effect (dose-obliteration, dose-complication, dose-bleeding) relationship has yet to be determined. When a linear accelerator is used to treat large AVMs, the difference between the effective radiation dose and the dose that causes complications is very small. However, three of the four models examined by Karlsson for analyzing dose-obliteration relationships used in the context of treating AVMs by SRS yielded satisfactory results for predicting the total number of obliterations [Karlsson et al., 1999]. In two of these three models, the accuracy in predicting the probability of obliteration depended on the size of the AVM and the dose. Only one model gave this prediction independently of these two parameters and of the others examined, except in the case of a dose administered at the periphery of the AVM.

TABLE 1

Results of studies examining various types of SRS treatment for vascular lesions

AUTHORS	TYPE OF STUDY	TYPE OF SRS	NUMBER OF PATIENTS (TYPE OF LESIONS)	PRIOR TREATMENT	MEAN DURATION OF FOLLOW-UP (IN MONTHS)	DOSES (GY)	EFFECTIVENESS OF THE TREATMENT	COMPLICATIONS	AUTHORS' CONCLUSIONS
Kondziolka et al. 1995	Case series	GK	47 (cavernomas)	N.S.	43 (4 to 77)	16	Significant reduction in the number of hemorrhages	Neurological deterioration: 26%	Effective treatment Complications often moderate and yield to medical treatment.
Young et al. 1997	Retrospective	Linear accelerator	50 (AVMs)	Surgery: 3 Embolization: 17 Embolization and surgery: 6	50	12 to 25	Obliterations (31/45)	Epileptic seizures (1) Worsening of memory (1)	Effective treatment.
Amin-Hanjani et al. 1998	Case series	Proton therapy	95 (cavernomas)	N.S.	64 (4 to 148)	15 to 16.5	- Significant reduction in the hemorrhage rate - Improved seizure control	Incidence of permanent neurologic deficit: 16% Mortality rate: 3%	Effective treatment, but potential for complications and continued lesion progression.
Chang et al. 1998	Case series	Helium ions (47) Linear accelerator (10)	57 (vascular malformations not detected by angiography)	N.S.	90 (9 to 164)	18 (7 to 40)	Significant reduction in the annual bleed rate determined 3 years after treatment.	10.5% (6/57, namely, edema (2), necrosis (1) and increased seizure frequency (1)	Effective treatment.
Miyawaki et al. 1999	Retrospective	Linear accelerator	73 (AVMs)	Surgery: 10 Embolization: 43 SRS: 2	Median: 72 (for 46 subjects in whom efficacy criteria were met) Median: 71 (39 to 93) (46 subjects in whom efficacy criteria were not met)	16 (10 to 22)	Obliterations 28/60	- Immediate: 16% - Late: 49% - 13 patients out of 73 required medical or surgical treatment	To optimize safety and efficacy, one must carefully select the candidates, ensure the accuracy of the digital images and dosimetry, and provide a regular follow-up.

AVM: Arteriovenous malformation; GK: Gamma knife; [1]N.S.: Not specified.

4.2 BRAIN TUMORS

4.2.1 Brain metastases

Brain tumors, in particular, brain metastases, are one of the main indications for SRS. However, most studies have involved patients with no more than two metastases, and the use of SRS for primary malignant tumors is fairly limited. This is due to the fact that malignant tumors are often invasive, which requires a more appropriate treatment (conventional fractionated radiotherapy).

Nearly 50% of cancer patients will develop brain metastases. In one third of these cases, the metastases will cause neurological symptoms. Brain metastases are the most frequent intracerebral tumors. Although the figures vary according to the author, the [illegible] dence of brain metastases is estima[illegible] to 12 cases per 100,000 populati[illegible] 1999] (Table G.1A in Appendix G). [illegible] e-tastases progress to death in a consider[illegible]ole number of cases. Young et al. report a mortality rate of more than 50% in patients treated with conventional radiotherapy [Young et al., 1995].

The studies are very heterogeneous. Most of them are actually case reports where the inclusion criteria are not clearly defined. Quality control or the validation process sometimes lacked methodological rigour [Auchter et al., 1996; Boyd and Mehta, 1999; Breneman et al., 1997]. A description of the studies examined is provided in Table 2.

TABLE 2

Results of studies examining SRS for brain metastases

AUTHORS	TYPE OF STUDY	TYPE OF SRS	DURATION OF FOLLOW-UP	NUMBER OF PATIENTS	NUMBER OF METASTASES	PRIOR RADIOTHERAPY (% OF SUBJECTS)	DOSES (GY)	TUMOR CONTROL	COMPLICATIONS	NUMBER OF BRAIN DEATHS	AUTHORS' CONCLUSIONS
Alexander et al. 1995	Retrospective	Linear accelerator	26 months (median)	248	421	100	15 (median)	85% (1 year) 65% (2 years)	N.S.*	N.S.	SRS as effective as surgery.
Auchter et al. 1996	Prospective, multicentre	Linear accelerator	28 months	122	122	100	17 (10 to 27)	86%		35	SRS comparable to external radiotherapy and surgery (even better in terms of survival). Results debated because of a certain bias with regard to sampling, the methodology, duration of follow-up and study parameters.
Breneman et al. 1997	Cohort follow-up	Linear accelerator	N.S.	84	177	96	16 (10 to 22)	25%	7[4], 2[5]	8	SRS comparable to surgery and superior to external radiotherapy. SRS effective for recurrent metastases.
Flickinger et al. 1994	Cohort follow-up	GK	7 months (median)	116	116	56	17.5 (8 to 30)	85%	4[1]; 1[2]; 3[3]	0	SRS effective in patients with a solitary brain metastasis.
Foote et al. 1999	Cohort follow-up	Linear accelerator	16 months	166	N.S.	> 90	15 (10 to 17.5)	86%	8[2]	N.S.	SRS effective.
Joseph et al. 1996	Cohort follow-up	Linear accelerator	8 to 50 months	120	189	83	26.6 (10 to 35)	96%	202	25	SRS is as effective as surgery. In the case of multiple metastases (more than 3), SRS is as effective as external radiotherapy.

TABLE 2

Results of studies of SRS for brain metastases (Cont'd)

AUTHORS	TYPE OF STUDY	TYPE OF SRS	DURATION OF FOLLOW-UP	NUMBER OF PATIENTS	NUMBER OF METASTASES	PRIOR RADIOTHERAPY (% OF SUBJECTS)	DOSES (GY)	TUMOR CONTROL	COMPLICATIONS	NUMBER OF BRAIN DEATHS	AUTHORS' CONCLUSIONS
Kihlstrom et al. 1993	Retrospective	GK	More than 1 year	160	235	N.S.	27 (10 to 56)	94% (66% in 3 to 6 months)	9[1]; 4[2]	16	GK more effective than surgery and external radiotherapy. Fewer complications.
Kim et al. 1997	Retrospective	GK	8 months (mean, with maximum of 60 months)	77	115	92	16 (10 to 22.5)	88%	2[1]; 1[2]; 2[3]	15	SRS effective and causes few complications.
Mori et al. 1998	Retrospective	GK	11 months (0.5 to 56 months)	35	52	80	17 (13 to 20)	90%	1[2]	4	SRS is effective and improves quality of life.
Shiau et al. 1997	Retrospective	GK	12 months	100	219	83	18.5 (10 to 22)	77% (1 year)	2[2]	N.S.	The dose-effect relationship has a determining influence on therapeutic outcomes.
Valentino 1995	Retrospective	Linear accelerator	2 to 8 years	139	139	0	50 (to 15 to 80)	92%	N.S.	N.S.	The effectiveness of the treatment cannot be predicted on the basis of the number of metastases. No significant difference in survival in patients with at least two tumors.
Young et al. 1995	Cohort follow-up	GK	5 to 17 months	107	288	100	21 (10 to 40)	91%	4[1]; 1[3]	6	Efficacy comparable to that of surgery; improved quality of life.

[1]Edema; [2]Radiation necrosis; [3]Hemorrhage; [4]Epileptic seizures, edema; [5]Radiation necrosis requiring reintervention; [6] Injury to cranial nerves
•N.S.: Not specified; GK: Gamma knife

The preliminary results of studies of the treatment of brain metastases by SRS using a dedicated linear accelerator in 12 patients were reported by Sturm et al., and they were encouraging. SRS slowed the progression of the tumor and reduced its volume. The authors proposed SRS as the treatment of choice for inoperable and radioresistant metastases.

Since then, numerous studies have been carried out [Foote et al., 1999; Kim et al., 1997; Shiau et al., 1997; Joseph et al., 1996; Alexander et al., 1995; Valentino, 1995; Kihlstrom et al., 1993;] (Table 2). Their results support the initial observations. The researchers successfully controlled tumor progression in 80% of the cases (25 to 97%) and obtained a fairly high survival rate in the patients (6 to 15 months), according to the review carried out by Boyd and Mehta covering 21 case series, 1,783 patients and more than 2,724 lesions [Boyd and Mehta, 1999]. According to their review, the factors that determine the efficacy of SRS are age (under 60 years), Karnofsky's index (greater than 70), control of the primary tumor, single location (brain) and the number of metastases (fewer than three). Very few studies have investigated the treatment of multiple metastases (generally from two to four) by SRS. The results of these rare studies confirm that SRS is potentially useful in the treatment of multiple brain metastases.

- When used in combination with standard treatments or surgery, SRS is effective and results in decreased morbidity [Muacevic et al., 1999; Mori et al., 1998; Jokura et al., 1994; Vecht et al., 1993]. Grob et al. report an improvement in quality of life in the patients treated by SRS (Karnofsky's index of 80%) [Grob et al., 1998].
- SRS could be an alternative in the treatment of tumors located near critical structures or even a first-line approach for radioresistant brain metastases [Feuvret et al., 1999].
- SRS can be an effective alternative in the treatment of small tumors and residual or recurrent tumors after surgery, and for preserving cranial nerve integrity.
- Although there is little information on this, SRS might be useful in the treatment of brain tumors in children [Edwards-Brown and Jakacki, 1999].
- SRS offers better cost-effectiveness than surgery with regard to CNS metastases [Loeffler et al., 1999].

The Radiation Therapy Oncology Group (RTOG) in Philadelphia determined the maximum dose of single-fraction radiation in 102 patients who had previously been treated by conventional radiotherapy and whose primary brain tumor or metastases had reappeared. The participants, who were recruited at 16 facilities, were treated between 1990 and 1993. In their conclusion, the authors state that the following two variables are associated with the occurrence of neurotoxicity manifestations [Shaw et al., 1996]:

- The target volume, if it is greater than 8,200 mm^3.
- The maximum dose/prescribed dose ratio: When the ratio of the maximum dose absorbed by a tumor of a given volume to the prescribed dose is greater than or equal to 2, it provides information about the heterogeneity of the radiation dose that reaches the target. The doses varied according to the treatment group and the technology used (assignment to one of three groups, according to the size of the tumor). Other authors, such as Nedzi [Nedzi et al., 1991], have reported such a relationship between neurotoxicity and tumor dose heterogeneity.

In its report, the RTOG notes that the same heterogeneity is observed with single-isocentre treatment and that, in this study, most such treatments were administered by means of a linear accelerator. Nonetheless, it cannot be concluded from this observation that one technology is superior to another. Other similar results have been reported [Engenhart et al., 1993].

In conclusion, all the results of the studies concerning brain metastases support the safety and efficacy of SRS in certain carefully se-

lected cases. The main advantage of this type of treatment over conventional radiotherapy is the improvement in the patient's quality of life. However, results of randomized studies are needed before it can be categorically concluded that SRS is effective for brain metastases. In addition, SRS is still not an appropriate form of adjuvant treatment to conventional radiation of the brain in patients with progressive systemic cancer.

The advantages of the gamma knife in the treatment of brain metastases are not due to its biological efficacy but rather to its technical and practical aspects, for it is easier to treat several targets with a gamma knife. On the other hand, irradiating several isocentres with an adapted linear accelerator is a relatively complex procedure [Ganz et al., 1991]. The complications associated with the gamma knife are rare or even nil. However, the characteristics and precision of the new generations of dedicated linear accelerators (micromultileaf) seem fairly similar to those of the gamma knife [Alexander et al., 1995; Kida et al., 1995; Rand et al., 1995].

4.2.2 Pituitary tumors

Thanks to advances in microsurgery and to improvements in approach techniques (transsphenoidal), neurosurgery is the treatment of choice for pituitary adenomas. The recurrence rate is generally low during the 5 to 10 years after complete surgical excision, and the incidence of serious complications (e.g., loss of cerebrospinal fluid, meningitis, diabetes insipidus or even hypopituitarism) is approximately 10%. The best outcomes are achieved at specialized centres with more experience in the surgical excision of secreting microadenomas (low recurrence and/or complication rate). However, even at these centres, the level at which the growth hormone concentration is considered satisfactory is not always achieved (15 to 20% of microadenomas and 40 to 50% of macroadenomas). Adjuvant treatment is often necessary (radiotherapy or medical treatment) [Clayton et al., 1999].

Presently, certain types of radiotherapy seem to be good alternatives for patients who are not amenable to surgery and in the treatment of surgically refractive tumors.

Many study reports state that conventional radiotherapy is effective in the treatment of pituitary adenomas. The average dose usually administered is 45 Gy (fractionated into 25 doses of 1.8 Gy/day) and, with time, offers good efficacy (tumor control in 90% of cases) [McCord et al., 1997; Tsang et al., 1996; McCollough et al., 1991; Sheline and Tyrell, 1984]. However, since a tumor takes a relatively long time to respond to this type of treatment and since the time to the onset of adverse effects or immediate or late complications complicates the follow-up [Eastman et al., 1979], conventional radiotherapy is of limited usefulness in treating this type of tumor [Estrada et al., 1997; Tsang et al., 1996; Sheline and Tyrell, 1984; Pistenma et al., 1976; Edmonds et al., 1972].

According to scarce published study results, the use of proton particle accelerator, gamma knife or linear accelerator SRS in the treatment of pituitary adenomas results in stabilized or even decreased hormone secretion in the medium or longer term [Fabrikant et al., 1992]. The main studies examined are summarized in Table 3.

TABLEAU 3

Results of studies of SRS for pituitary tumors

AUTHORS	TYPE OF STUDY	TYPE OF SRS	PRIOR SURGICAL TREATMENT	DURATION OF FOLLOW-UP	NUMBER OF PATIENTS	TYPE(S) OF TUMOR	DOSES (GY)	CURE OR IMPROVEMENT/ TUMOR CONTROL	AUTHORS' CONCLUSIONS
Fabrikant et al. 1992	Case series	Helium ions	20%	1 to 30 years	318	S	30 to 50	• Most (cure) 70% decrease in STH level after 1 year for most of the tumors	No comment.
			?	1 to 30 years	34	NS	?	• The vast majority (control)	
Kjellberg and Abbe 1988	Case series	Proton therapy	?	1 to 25 years	551	S	40 to 150	93% (cure)	No comment.
			?	1 to 25 years	154	NS	10 to 70	Nearly all	
Lunsford et al. 1995	Case series	GK	82%	3 to 72 mos	14	S	10 to 30	64% (cure) 95% (control)	The gamma knife seems to be an effective treatment (alternative or adjuvant).
			?	3 to 72 mos	12	NS	10 to 30	95% (control)	
Rocher et al. 1995	Case series	Linear accelerator	100%	9 to 31 mos	6	S	20	67% (cure or improvement) 81% (control)	The use and efficacy of the linear accelerator depend on the type and nature of the tumor.
			100%	9 to 31 mos	15	NS	20	81% (control)?	
Thoren et al. 1991	Case series	GK	62%	1 to 21 years	21	S	70 to 100	38%	The use and efficacy of the linear accelerator depend on the type and nature of the tumor.
			0%						
Voges et al. 1996	Case series	Linear accelerator	94%	8 to 40 mos	12	S	8 to 20	50% (control) Decrease in STH level from 17 to 5 µg/L	The linear accelerator is effective. The effective dose depends on the type of tumor.
			?	8 to 40 mos	4	NS	8 to 20	100%	

GK: Gamma knife, S: Secreting tumors, NS: Nonsecreting pituitary tumors, STH: Somatotrophic hormone

In a comparative study of the treatment of pituitary tumors (specifically, prolactinomas and Cushing's disease), McCord et al. reported a tumor control rate (reduction in tumor volume and hormone secretion) of close to 90% [McCord et al., 1997]. The other studies do not permit any definitive conclusions [Lunsford et al., 1995; Kjellberg and Abbe, 1988] or yielded results that were not very encouraging (e.g., Nelson's syndrome) [Voges et al., 1996].

In most of the cases examined, SRS was a type of adjuvant treatment to the surgical excision of pituitary tumors. Lesions invading the dura mater and bone, which are characterized by a high recurrence rate, are among the indications for SRS [Laws and Vance, 1999].

Complications of SRS are rare [Landolt et al., 1998] and are usually due to the nature of the tumor. The various types of complications range from hypopituitarism (0 to 55% of cases) to a loss of visual acuity (1 to 39% of cases). A decrease in the incidence of these complications is associated with an increase in the quality of medical images and the radiation doses administered [Rocher et al., 1995; Levy et al., 1991; Rähn et al., 1991; Thoren et al., 1991; Coffey and Lunsford, 1990; Degerblad et al., 1986; Kjellberg and Abbe, 1988]. The hypothalamic lesions reported are sometimes serious (malignant hypothalamic syndrome [Voges et al., 1996]) or even fatal [Lunsford et al., 1995].

Methodological problems (e.g., the diversity of the biological criteria for cure) and the contradictory results obtained by various authors have contributed to creating some confusion regarding the usefulness of SRS in the treatment of radiotherapy-resistant pituitary adenomas (acromegaly, Cushing's syndrome, prolactinoma). The following observations are worth mentioning:

- The validity of the conclusions is limited by the small population in most of the studies.
- Time to tumor response to radiotherapy is associated with the tumor's hormonal and anatomical characteristics.
- The efficacy of SRS in treating pituitary tumors and the occurrence of adverse effects are much debated. Little use is still made of SRS for pituitary adenomas, especially if the optical structures cannot be visualized [Ganz et al., 1993]. The use of the gamma knife (at doses less than 10 Gy) for invasive tumors of the cavernous sinus makes the treatment potentially safer for the optical structures. However, a longer follow-up should be conducted to assess the effectiveness of the treatment, its effects on physiological functions and its complications [Jackson and Norén, 1999].
- Other constraints to SRS concern retreatment. For example, exposing the optic chiasma to a dose of 8 Gy results in a loss of visual acuity.
- Using a linear accelerator in the treatment of pituitary adenomas presents certain difficulties because of what is required to recalibrate the instrument. This concerns the individuals involved (patient's cooperation, operator's experience) as well as the equipment (instrument's intrinsic requirements) [Nataf et al., 1998]. The technical performance of the new generations of dedicated linear accelerators is reportedly comparable to that of the gamma knife.

Conclusions

- Even if it theoretically seems preferable to treat pituitary adenomas with SRS (specifically, by gamma knife), surgical excision (microsurgery through a transsphenoidal approach) is opted for in most cases. Unlike SRS, surgical excision permits the rapid correction of hormone hypersecretion.
- Even if the long-term follow-up results of most studies have not yet been disseminated (the time it takes to assess the efficacy of a given treatment is long and depends on the type of tumor: 3 to 4 years in the case of acromegaly, 2 to 2.5 years in the case of Cushing's syndrome), it seems that SRS causes fewer complications than conventional radiotherapy.

- Given the advances in SRS, we can expect considerable improvement in the health of individuals with such tumors, mainly because of its efficacy in reducing hormone hypersecretion. In this respect, the gamma knife acts faster than conventional radiotherapy.
- The gamma knife is effective in the treatment of pituitary tumors that resist surgical treatment following conventional radiotherapy and in the treatment of microadenomas and noncompressive sellar tumors when the patient refuses surgery or when the transsphenoidal approach is not possible.
- As for the comparison between the linear accelerator and the gamma knife, to date, no scientific data support the superiority of one over the other. The choice of type of radiotherapy (linear accelerator, gamma knife, conventional radiotherapy) depends on a number of factors, the main ones being the size, volume and location of the main tumor. In addition, it would seem that certain types of radiotherapy are more appropriate for specific types of pituitary adenomas and craniopharyngiomas. Some publications report that gamma knife radiosurgery is effective in the treatment of residual or recurrent craniopharyngiomas after surgical treatment.

4.2.3 Meningiomas

Meningiomas are slow-growing and generally noninvasive, benign tumors arising from arachnoid cells or, in the exceptional case, from ectopic meningeal cells (intraventricular meningiomas). They account for about 20% of all primary brain tumors. Meningiomas are more frequent in adults and occur in twice as many women as men. Their clinical picture varies (hemiparesis, seizures, a loss of visual acuity, aphasia, etc.) and depends on the tumor's location. The surgical excision of skull base meningiomas (sphenoid or cavernous sinus) is a very delicate procedure [Black, 1993; Al-Mefty et al., 1988; Modan et al., 1974].

Although improvements made to the neurosurgical approach have reduced the mortality rate to less than 10%, the number of postoperative complications is still high. The same is true for the recurrence rate, which is high because of the tumor's inaccessibility and its adjacency to certain sensitive structures of the brain (the rate is about 10% over 10 years and can be as high as 50% in cases of partial excision) [Adegbite et al., 1983; Al-Mefty et al., 1988]. The use of adjuvant radiotherapy to partial excision has improved these outcomes [Barbaro et al., 1987; Condra et al., 1997; Goldsmith et al., 1994; Mesic et al., 1986; Petty et al., 1985; Solan and Kramer, 1985; Taylor et al., 1988]. Conventional radiotherapy proved relatively effective [Busse, 1991] but also of limited usefulness [Black, 1993]. SRS then served as an adjunct to and improved the treatment of meningiomas and the prevention of the complications of radiotherapy.

Based on the results of studies of the use of the gamma knife for meningiomas, gamma knife SRS compares with the standard treatments (surgery and conventional radiotherapy alone or in combination) and permits better tumor growth control, with rates of between 87 and 100% of patients, and improved functional status, with rates from 87 to 92% of patients [Kondziolka et al., 1999; Subach et al., 1998; Kurita et al., 1997; Pendl et al., 1997; Steiner et al., 1997]. Since SRS is less toxic than conventional radiotherapy, it is better suited for the treatment of cavernous sinus and skull base meningiomas [Liscak et al., 1999a; Maguire et al., 1999; Morita et al., 1999]. However, it is not without risks and can cause, among other things, neuropathies if the administered doses are greater than 19 Gy (greater than 10 Gy in the case of ophthalmic complications due to optic nerve injury) [Morita et al., 1999; Subach et al., 1998; Kurita et al., 1997]. However, long-term results are scarce.

The results of studies of the treatment of meningiomas by linear accelerator are similar to those for the gamma knife (Table 4) [Colombo and Francescon, 1998; Hakim et al.,

1998; Chang and Adler, 1997; Valentino et al., 1993]. The radiation doses administered ranged from 10 to 45 Gy, depending on the study [Shafron et al., 1999; Valentino et al., 1993]. Control of tumor progression varied from 89 to 98% during follow-ups ranging from 23 to 48 months. Most often, the results obtained depend on the characteristics of the lesion, its location (skull base, brain convexity, etc.), the adjuvant treatment and the treatment team's experience. The treatment of meningiomas by SRS seems effective in the long term [Debus et al., 1999].

With the exception of the study by Engenhart et al. [Engenhart et al., 1990], which revealed serious complications due to the administration of high doses of radiation, the complications observed are usually transient [Colombo and Francescon, 1998; Hakim et al., 1998; Valentino et al., 1993]. However, serious lesions (radiation necrosis together with symptomatic peritumoral edema) and deaths have been reported (linear accelerator SRS) [Chang et al., 1998a; Hakim et al., 1998].

Improvements to digital imaging are permitting better monitoring of tumor evolution after treatment and a better assessment of the efficacy of the different treatment modalities, specifically, partial excision, total excision and partial excision in combination with radiotherapy, SRS, or radiotherapy and SRS at the same time.

In conclusion, and in light of the results of studies, which, however, offer a low level of evidence (case series), the following statements can be made:

- The optimal treatment of an intracranial meningioma requires complete excision of the tumor and dura mater [Kondziolka et al., 1999b]. Such treatment is possible in a certain number of patients, but in some cases, the tumor's location (skull base) and its proximity to particularly delicate structures prohibit complete excision or expose the patient to considerable risk (serious neurological disorders).
- SRS (by linear accelerator or gamma knife) seems safe and generally effective in controlling meningiomas. However, studies indicate that the outcomes depend on the tumor's characteristics (location, volume).
- The treatment of meningiomas depends on many factors, including the nature and location of the tumor, and the treatment team's experience.
- Malignant meningiomas nonetheless require a therapeutic approach that may include excision, conventional radiotherapy and stereotactic radiotherapy.

TABLE 4

Results of studies of SRS for meningiomas

AUTHORS	TYPE OF STUDY	TYPE OF SRS	PRIOR TREATMENT*	MEAN DURATION OF FOLLOW-UP	NUMBER OF PATIENTS	DOSES (GY)	TUMOR CONTROL (% OF CASES)	AUTHORS' CONCLUSIONS
Chang et al. 1997	Case series	Linear accelerator	Surgery: 38 Radiotherapy: 5	48 months (17 to 81)	55	18.3 (12 to 25)	98%	Two cases of radiation necrosis.
Colombo et al. 1998	Case series	Linear accelerator	Surgery: 47	33 months (4 to 144)	15	22.3 (18 to 26)	75% (at 8 years)	Two cases of loss of visual acuity (due to the proximity of the tumor to the optic chiasma).
Engenhart et al. 1990	Case series	Adapted linear accelerator	Surgery: 13	40 months (1 to 60)	17	29 (8 to 40)	100%	Four cases of complications, including one death due to SRS.
Hakim et al. 1998	Case series	Dedicated linear accelerator	Surgery: 105 Radiotherapy: 15	31 months (1 to 80)	127	15 (9 to 20)	89% (at 5 years)	Study involving all meningiomas, including malignant ones.
Shafron et al. 1999	Case series	Dedicated linear accelerator	Surgery: 32 Radiotherapy: 1	23 months (2 to 88)	70 (76 tumors)	12.7 (10 to 20)	Of 48 lesions (duration of follow-up: at least 1 year): reduction in volume: 21/48 (44%); no change: 27/48 (56%)	Two cases of neurological complications. Longer follow-up recommended in order to assess the efficacy of SRS for meningiomas more thoroughly.
Kurita et al. 1997	Case series	GK	Surgery: 15	34.8 months (6 to 72)	25	17 (12 to 22.5)	86% (at 5 years)	Six cases of complications, including one of permanent neurological deterioration.
Pendl et al. 1997	Case series	GK	Surgery: 53	18.5 months (6 to 46)	78	13.8 (7 to 25)	96%	The gamma knife is effective.
Steiner et al. 1997	Case series	GK	Surgery: 104	12 to 72 months	151	14 (10 to 20)	89%	The gamma knife is effective.
Subach et al. 1998	Case series	GK	Surgery: 39 Radiotherapy: 7	24 months (4 to 95)	62	15 (11 to 20)	87% (at 8 years)	Five cases of complications, including three of permanent neurological deficit.
Valentino et al. 1993	Case series	Linear accelerator[1]	Surgery: 38	48 months (30 to 96)	72	37 (1 to 4 fractions)	94%	Radiotherapy effective in stereotactic conditions (linear accelerator) against meningiomas.

1 Radiotherapy under stereotactic conditions. GK Gamma knife

4.2.4 Vestibular schwannomas

Vestibular schwannomas (VSs), or auditory nerve neurinomas, account for 10% of primary brain tumors. They are due to the proliferation of cells in Schwann's sheath, mainly on the vestibular segment of the 8th pair of cranial nerves (vestibulocochlear, or auditory nerve). The location of these tumors (posterior fossa) and their proximity to extremely sensitive structures (cranial nerves, brain stem) explain the relatively serious postoperative complications and even the deaths that occur in the best of conditions and despite the most expert of hands [Foote et al., 1995].

A better knowledge of neurinomas, the evolution of microsurgery and the use of new surgical approaches have lead to considerably better outcomes of surgical excision. The results of various studies indicate substantial improvement in the patient's clinical status following surgical treatment and a marked decrease in complications [Ebersold et al., 1992].

Among the more positive results are those of the study by Samii et al. [Samii and Matthies, 1997a, 1997b, 1997c], which involved 1,000 patients. Complete excision was performed in 98% of the cases, and the recurrence rate was 1% in the patients without type II neurofibromatosis (the duration of follow-up is not indicated). However, it should be noted that there was a considerable number of complications due to the treatment (loss of facial nerve integrity [7th pair] in 7% of the cases, facial nerve deficit in 47% of the cases, etc.) and deaths (11 deaths, or 1% of the cases). These results are indicative of the limitations of surgical treatment for this type of tumor.

Although conventional radiotherapy is not routinely used for VSs, the results of the odd study in this area are encouraging. Mention should be made of the study by Wallner et al. [Wallner et al., 1987], which involved 33 patients with VSs treated by surgical excision. The tumor reappeared in 46% of the patients treated solely by surgery (6/13) and 15% of those who had received treatment consisting of surgery plus radiotherapy (3/20). The number of recurrences in the surgery-and-radiotherapy group suggests that there is a relationship between the efficacy of the treatment and the administered dose (in two-thirds of the cases of recurrence, the dose was less than 45 Gy, whereas the tumor reappeared in only 1 of the 17 patients who had received a dose greater than 45 Gy).

VSs were treated by SRS for the first time in 1969 by the neurosurgeon Leksell. The study was conducted at the Karolinska Institute in Stockholm and involved three cases treated by gamma knife [Leksell, 1971a]. Many other studies have been published since then [Lederman et al., 1999; Norén, 1998; Lunsford et al., 1997; Flickinger et al., 1996; Ogunrinde et al., 1995; Linskey et al., 1993; Norén et al., 1993; Linskey et al., 1990]. The various published study reports and case reports mention adverse effects or late complications.

A retrospective study involving the treatment of 402 cases of VS by gamma knife radiosurgery (including 97 cases treated unsuccessfully by surgical excision) and a mean duration of follow-up of 36 months (up to 7 years) found that the lesions evolved favourably and showed the importance of medical imaging quality in reducing radiation-induced complications and improving treatment [Lunsford et al., 1997].

Table 5 summarizes the results of nine studies of the treatment of VSs by SRS. Based on these results, which also concern the use of the adapted linear accelerator [Valentino and Raimondi, 1995], SRS could be an alternative to the standard treatments (surgery and conventional radiotherapy). However, the conclusions of a recent meta-analysis by Kaylie [Kaylie et al., 2000] contains certain reservations as to attributing any advantages to either of the approaches (microsurgery or gamma knife SRS) because of often incomplete and imprecise data and because of the lack of standards for comparing the studies with each other.

TABLEAU 5

Results of studies of SRS for vestibular schwannomas

AUTHORS	TYPE OF STUDY	TYPE OF SRS	DURATION OF FOLLOW-UP (MONTHS)	NUMBER OF PATIENTS	TUMOR VOLUME (CM^3)	MEAN ADMINISTERED DOSE (GY)	TUMOR EVOLUTION (% OF CASES)			COMPLICATIONS (CT AND MRI)		
							Regression	**Stabilization**	**Growth**	**Facial neuropathies (%)**	**Trigeminal neuropathy (%)**	**Other (%)**
Lunsford et al. 1998	Case series	GK	36 to 84	402	N.S.	2 to 14	30	63	7	28	34	8
Schafron et al. 1998	Case series	Linear accelerator	12 to 94	101	4.7	10 to 22.5	55	39	6	14	11	13
Norén et al. 1998	Case series	GK	35 (10 to 67)	71	N.S.	13.6 (8 to 20)	51	42	7	14	8	N.S.
Ito et al. 1997	Case series	GK	39 (4 to 73)	46	1.6	16.8 (12 to 25)	22	74	4	22	30	N.S.
Flickinger et al. 1996	Case series	GK	13 (CT) 47 (MRI)	118 155	3.5 2.7	17 14	39	53	9	27 7.6	36 7.6	N.S.
Foote et al. 1995	Case series	GK	2.5 to 36	36	3.1 (0.26 to 8.6)	16 to 20	26	74	0	22	30	N.S.
Valentino and Raimondi 1995	Case series	Linear accelerator[1]	40 (24 to 96)	23	6.7	30 (12 to 45)	38	58	4	4	4	4
Kobayashi et al. 1994	Case series	GK	12 (3 to 20)	44	6.2	14.8	25	75	0	16	7	8.5
Martens et al. 1994	Case series	Linear accelerator	19 (12 to 24)	14	1.9	19.4 (16 to 20)	29	71	0	21	14	N.S.

N.S.: Not specified, GK: Gamma knife, CT: Computed tomography, MRI: Magnetic resonance imaging

1. Radiotherapy under stereotactic conditions

In addition, in another comparative study, this one of watchful waiting and fractionated stereotactic radiotherapy for VSs, the tumor grew more slowly in the patients who had received prior treatment [Shirato et al., 1999].

The standard treatment for the other types of schwannomas consists of surgical excision. However, the efficacy of SRS against this type of tumor [Pollack et al., 1993], the complications associated with surgery, and patient status (advanced age, comorbidity), support the use of SRS as an alternative.

In their article on the treatment of VSs by gamma knife, Ross and Tator [Ross and Tator, 1998] suggest that with no gamma knives in Canada, these tumors will have to continue to be treated in accordance with the current protocols, with reimbursement of gamma knife treatments performed outside the country.

In conclusion, SRS seems to be an appropriate therapeutic approach for VSs, given its relative safety and its precision. This treatment modality, specifically, the use of the gamma knife, could be an alternative for overcoming the interventional difficulties that the standard treatments pose and for preventing their complications.

4.2.5 Gliomas

Primary tumors of the nervous system are mainly gliomas. Malignant gliomas, especially glioblastomas multiforme (80% of malignant gliomas), have a polymorphic nerve architecture characterized by a large number of cellular constituents (proliferation of atypical glial cells). Microscopically, one often observes necrotic and hemorrhagic areas. Gliomas can arise from the transformation of benign glial tumors, such as astrocytomas. Metastases are rare or even very rare and infiltrative [Wallner et al., 1989]. In the United States, nearly 7,000 new cases are reported each year.

The survival of an individual with untreated glioblastoma multiforme is estimated to be three months [Salcman, 1980]. Treatment combining surgical excision and conventional radiotherapy extends survival to 9 or 10 months, with a 5% survival rate 5 years after diagnosis [Mehta, 1997]. The various proposed therapeutic approaches (surgery, radiotherapy, brachytherapy, hyperthermia and, more recently, fractionated stereotactic radiotherapy) yield more or less satisfactory results.

The results of a retrospective, multicentre study of the efficacy of SRS in controlling tumor progression and of the impact of this technique on survival sparked debate [Sarkaria et al., 1995]. This is because study participant selection was biased, given that the candidates considered had previously been treated with a combination of surgery and conventional radiotherapy.

The results of other studies of SRS for gliomas indicate widely varying efficacy (Table 6). However, all the results show that SRS is safe and effective as adjuvant treatment for glioblastomas.

In short, despite the fact that there are no comparative studies from which we could compare the efficacy of the various instruments used, SRS seems to be a promising approach to the treatment of gliomas (prolongs survival in patients with malignant gliomas).

TABLEAU 6

Results of studies of SRS for gliomas

AUTHORS	TYPE OF SRS	TYPE OF STUDY	NUMBER OF PATIENTS	TYPE OF TUMOR	DOSES (GY)	DURATION OF FOLLOW-UP AFTER SRS	COMMENTS
Alexander and Loeffler 1998	Linear accelerator	Case series	78	GBM	13	19.9 months	Reintervention necessary in 22% of the cases.
Coffey et al. 1993	GK	Case series	18	Primary malignant tumor	15 (12 to 18)	10 months (2 to 29)	Although the tumor regressed in 50% of the cases, the duration of survival was limited.
Gannett et al. 1995	Linear accelerator	Case series	30	19 GBM 11 ast.	10 (0.5 to 18)	GBM: 13 months Ast.: 28 months	Reintervention necessary in 33% of the cases.
Hall et al. 1995	Linear accelerator	Case series	35	26 GBM 9 ast.	28 (2.4 to 98)	GBM: 8 months Ast.: 12 months	Radiation necrosis observed in 5 cases (reintervention in 31% of the cases).
Kondziolka et al. 1997	GK	Case series	107	64 GBM 43 ast.	15.5 (12 to 25)	GBM: 16 months Ast.: 21 months	Reintervention necessary in 19% of the cases.
Sarkaria et al. 1995	Linear accelerator	Retrospective, multicentre	116	96 GBM 19 ast.	6 to 20	GBM: 22 months Ast.: N.S.	Results debated because of significant selection bias.
Shafron et al. 1999	Linear accelerator	Case series	76	49 GBM 19 ast.	13 (10 to 20)	GBM: 11.6 months Ast.: 11.4 months	Reintervention necessary in 24% of the cases. Survival apparently comparable for both types of tumors.

N.S.: Not specified; GK: Gamma knife; Ast.: Astrocytoma; GBM: Glioblastoma multiforme.

4.3 TRIGEMINAL NEURALGIA

There are two types of trigeminal neuralgia—essential and that due to an underlying lesion [Regis et al., 1999a].

The first individuals with functional disorders who underwent gamma knife surgery had trigeminal neuralgia [Leksell, 1971a] or Parkinson's disease [Lindquist et al., 1991]. In the case of trigeminal neuralgia, the target was the gasserian ganglion. Thirteen of the 22 patients treated experienced a decrease in pain within the following 6 months and three within 2.5 years. Despite this low remission rate, the authors concluded in favour of SRS [Leksell, 1971b]. This type of treatment was discontinued because of the advent of new effective drugs and the inadequacy of the imaging techniques (poor follow-up because of image resolution). The discovery, by Hakanson [Hakanson, 1981], of the glycerol effect (glycerol is used as a developer) provided a second impetus for discontinuing SRS.

The evolution of MRI has made reassessment of SRS possible [Regis et al., 1999b]. One of the most important case series has been that at the University of Pittsburgh. Its results showed that pain disappeared (essential trigeminal neuralgia) in 64 of the 106 patients (60%) who were followed [Kondziolka et al., 1998]. These results do not seem as good as those yielded by the other treatments (glycerol neurolysis [glycerolysis], thermocoagulation, surgical or balloon vascular microdecompression). It should be noted that the patients admitted to the study were treated after failure with the other treatments.

The technical approach and the doses administered in the treatment of trigeminal neuralgia can vary. Better outcomes were achieved when the target was the retrogasserian segment of the nerve (apparent origin of the nerve) rather than the posterior root entry zone, and when the administered dose was higher (90 Gy) [Regis et al., 1999a].

For other authors [Young et al., 1998b], the gamma knife is currently the most effective and safest method of treating trigeminal neuralgia. They point out that the earlier the treatment, the better the outcome. However, a clear diagnosis must be made. The gamma knife's safety could be an important factor in favour of SRS as adjuvant treatment for refractory trigeminal neuralgia.

In a multicentre study, Kondziolka et al. suggest that the gamma knife could be used as a first-line treatment for trigeminal neuralgia. Despite the mixed results with SRS for trigeminal neuralgia, the authors are of the opinion that there is probably a relationship between treatment efficacy and the radiation dose administered (a dose of at least 70 Gy giving the best results) [Kondziolka et al., 1996].

Given the results of studies of the treatment of trigeminal neuralgia due to skull base lesions, the contraindications to neurosurgical treatment or to conventional radiotherapy, and the low risk of complications of SRS, the latter could be an attractive alternative for this condition (Table 7).

Other forms of treatment for trigeminal neuralgia, such as percutaneous stereotactic thermal rhizotomy, are presently being investigated [Scrivani et al., 1999].

In conclusion, the new scientific data on trigeminal neuralgia, together with the improvements to digital imaging (MRI and CT), are broadening the horizon for the use of SRS, particularly gamma knife SRS, in the treatment of this pathology.

TABLE 7

Results of studies of SRS for trigeminal neuralgia

AUTHORS	PRIOR TREATMENT	NUMBER OF PATIENTS	DURATION OF FOLLOW-UP	DOSES (GY)	CHANGE IN PAIN (% OF CASES)	COMMENTS
Kondziolka et al. 1996[1]	Surgery: 32/50	50	18 months (11 to 36)	60 to 90	Disappeared: 58 Decreased: 36 No effect: 6	After 2 years, no pain in more than 50% of the cases.
Regis et al. 1995a[2]	Surgical and/or medical	20	N.S.	N.S.	Decreased: 82	• Results uninterpretable. Patients with several concurrent conditions. • Duration of follow-up not specified.
Young et al. 1998b[2]	Medical and/or surgical	110	19.8 months (4 to 49)	70 to 80 (max)	Disappeared: 95.5 (subjects who had not had prior surgical treatment [3.3% of them experienced recurrent pain during the same period]. 3 cases of delayed loss of facial sensation after SRS.	Conclusions concern the safety and efficacy of gamma knife SRS for trigeminal neuralgia.

Comment: There was no study about the use of the liner accelerator for the treatment of this pathology.
1. Prospective multicentre study; 2. Case series, N.S.: Not specified

4.4 OTHER PATHOLOGIES

4.4.1 Other tumors

A few authors discuss the use of SRS for glomus jugular tumors [Eustacchio et al., 1999; Liscak et al., 1999b]. They state that SRS is safe and that there are no acute or immediate complications. Since these tumors grow very slowly, the authors propose a longer follow-up in order to assess the efficacy of SRS in treating this type of tumor.

In a study of the treatment of ependymomas (tumors arising from the ependymal cells that line the walls of the ventricles of the brain), SRS resulted in tumor growth control in 68% of the participants on average (3 years) and in survival of 3.4 years (1.4 to 5 years) [Stafford et al., 2000]. It should be noted that 11 of the 12 patients had previously undergone surgical resection plus conventional radiotherapy. Two patients experienced complications.

SRS has been used for other tumoral processes, such as spinal cord malformations [Takacs and Hamilton, 1999], and as adjuvant treatment for cavernous sinus hemangiomas [Iwai et al., 1999] or hypothalamic hamartomas (floor of the third ventricle) associated with seizures [Arita et al., 1999]. Although SRS had beneficial effects, more-thorough studies are needed.

4.4.2 Parkinson's disease

To date, very few study reports on the use of SRS in the treatment of Parkinson's disease have been published. Most studies have concerned the use of the gamma knife in a small number of patients, and the results obtained have been mixed [Friedman et al., 1999; Ishikawa et al., 1999; Ohye et al., 1996; Rand et al., 1993; Lindquist et al., 1991].

In a study involving 17 patients with movement disorders (5 cases of Parkinson's disease, 12 cases of idiopathic tremor), Friedman et al. observed a decline in tremor (assessed by means of the Tremor Rating Scale) in all the patients (3 months after SRS) [Friedman, 1999]. They report complications in five cases. All the complications yielded to corticosteroid therapy. After eight months, two subjects treated by pallidotomy developed late complications (right hemiparesis with lesion visible on MRI, difficulty swallowing and hypophonia). According to the authors, these results suggest that SRS thalamotomy could be performed for tremor that is resistant to the usual medical treatments. The late occurrence of a few complications in some of the subjects who developed perilesional edema three months after treatment indicates the need for longer-term monitoring (at least one year).

The authors of a retrospective study which involved 34 patients note that the administration of high doses of radiation (160 Gy) is more effective and does not carry a risk of complications [Duma et al., 1999]. They arrived at similar conclusions for patients with movement disorders associated with major systemic diseases or coagulopathies [Young et al., 1998a].

Even if SRS has yielded promising results for Parkinson's disease, they need to be confirmed by comparing the different existing treatment modalities in rigorous studies. Furthermore, other types of treatment (e.g., electrical stimulation) for Parkinson's disease are presently being investigated and are yielding good results.

4.4.3 Epilepsy

The cessation of epileptic seizures observed in individuals with gamma knife-treated AVMs prompted the conduct of studies of the efficacy of SRS in the treatment of epilepsy [Lindquist et al., 1991; Lunsford, 1990; Heikkinen et al., 1989; Steiner and Lindquist, 1987].

Lindquist et al. [Lindquist et al., 1991] reported the cessation of epileptic seizures in 52 (89%) of the 59 individuals with gamma knife-treated AVMs. These results are comparable to those obtained with

brachytherapy and conventional radiotherapy [Whang and Kim, 1995; Alexander and Lindquist, 1993; Alexander and Loeffler, 1992; Loeffler and Alexander, 1990; Rossi et al., 1985]. Conventional surgical treatment results in seizure suppression in about 70% of cases [Spencer, 1996, Sperling et al., 1995; Engel, 1993; Rougier et al., 1992].

According to other study reports concerning the treatment of epilepsy, the gamma knife is as effective as microsurgery. However, patient follow-up is generally not long enough (an average of one year), with the result that there is a risk of recurrence. Patients should be followed for at least two years in order to arrive at a definitive conclusion [Elwes et al., 1991; Wingkun et al., 1991].

The mechanism of action of the gamma knife in the treatment of epilepsy has yet to be elucidated. In theory, it could reside in the following two effects:

- The destruction of epileptogenic foci and of their propagation tissues. This theory has been described experimentally [Ishikawa et al., 1999; Gaffey et al., 1981].
- An actual antiepileptic effect. The same effect was observed after the administration of nonnecrotizing doses (10 Gy) [Regis et al., 1996]. Chalifoux and Elisevitch hypothesized that irradiation inhibits the synthesis of proteins needed for the sustained triggering of spontaneous discharges [Chalifoux and Elisevitch, 1996-1997].

In conclusion, SRS for epileptogenic brain lesions is still reserved for a few treatment centres. Even if the findings suggest that this is an effective treatment modality, the results obtained need to be confirmed by randomized, comparative studies.

4.4.4 Obsessive-compulsive disorders

Two to three percent of the world population (50 million people) have obsessive-compulsive disorders (OCDs) [Sasson et al., 1997; Weissman et al., 1994]. They rank fourth among behavioural disorders in the United States [Meyers et al., 1984]. OCDs occur in people of all ages, and nearly two-thirds of these individuals experience major depression during their lifetime [Rasmussen and Eisen, 1992]. Usually, the clinical picture includes other anxiety disorders (e.g., phobias). Certain imaging techniques (positron-emission and single-photon emission tomography) have revealed a certain number of brain lesions in these individuals [Trivedi, 1996]. The pathophysiology of OCDs is still poorly known, but some authors suggest that a dysfunction of neuronal circuits (fronto-striatal-pallido-thallamo-frontal) plays a role in their pathogenesis [Baxter et al., 1992; Modell et al., 1989].

There are several options for treating anxiety neuroses, such as psychotherapy, the psychosocial approach, electroconvulsive therapy and psychosurgery (temporal lobe ablation; even if the efficacy of this modality has not been established in comparative studies, certain European countries still authorize this type of treatment). Between 60 and 80% of patients respond favourably to behaviour therapy alone or in combination with drug therapy. In 20 to 30% of cases, the addition of or a change in medication (e.g., a serotonin inhibitor) improves the patient's health. In other cases, the anxiety neurosis resists any drug therapy and constitutes an indication for psychosurgery [Jenike and Rauch, 1994; Rasmussen and Eisen, 1992].

Since the first indications were approved in 1935, the techniques have evolved enormously. With the advent of SRS, it became possible to treat while at the same time considerably reducing the risk and incidence of adverse effects. There is a wide range of approaches [Lopes and Soares, 1999]. Based on the data recently published by Lippitz et al. [Lippitz et al., 1999], it seems that thermocapsulotomy and gamma knife capsulotomy yield the same type of results. However, the authors note that numerous factors can bias the evaluation. In their opinion, these results should be interpreted with cau-

tion and confirmed by prospective studies. The risk of error may be of a subjective (e.g., measurement of images of lesions obtained by MRI) or clinical (e.g., interpatient anatomical variations) nature. The effectiveness of the treatments also depends on the cause of the condition, which is often not clearly identified.

Thus far, no evidence from comparative scientific studies supporting the use of the gamma knife for OCDs can be found in the rare publications on this subject. Furthermore, the specific target of the treatment is still very much debated.

4.5 SUMMARY OF THE EFFICACY OF SRS

Apart from the lack of randomized, comparative trials, it is noted that the various published studies are prospective (cohort follow-up), retrospective or case report studies. As a general rule, all the results of these studies support the efficacy of SRS in certain carefully selected cases. The main advantage of SRS over conventional radiotherapy is the improvement in the patient's quality of life. Because of its safety, SRS can play an important role in first-line treatment or as an adjuvant to the standard treatment modalities.

The indications for SRS that are generally accepted and supported by scientific studies are as follows:

- AVMs.
- Brain metastases. Brain metastases from extracerebral tumors seem to be a target of choice for SRS, especially radioresistant metastases, small tumors, residual or recurrent tumors after surgery, and when one seeks to preserve cranial nerve integrity.
- Meningiomas near sensitive structures.
- VSs. SRS, especially gamma knife SRS, could be an alternative for overcoming interventional difficulties and avoiding the complications of the standard treatments.

The use of SRS for pituitary adenomas and certain skull base tumors is promising and depends on many different factors, such as the nature and location of the tumor and the treatment team's experience.

The effects of SRS in patients with functional disorders are not always as convincing as the established benefits of this type of treatment for certain structural brain lesions. The use of SRS will therefore be limited until its efficacy is assessed in rigorous scientific studies.

The main indications for SRS that emerge from our study concur with those mentioned in the ANAES's conclusions [ANAES, 2000] and in those of the Alberta Heritage Foundation for Medical Research [Schneider and Hailey, 1998].

Because of the paucity of comparative data on the clinical efficacy of the gamma knife and the dedicated linear accelerator, it cannot be concluded that either of these instruments is superior to the other. However, the gamma knife does seem to offer the degree of precision required for treating small lesions near sensitive structures, such as the optic chiasma and brainstem, thanks to its technical characteristics. Furthermore, the vast majority of studies have examined the use of the gamma knife for specific pathologies, such as VSs. This picture could, however, change in light of the technological improvements made to the equipment (especially dedicated linear accelerators), which could increase their precision.

5 COMPLICATIONS

Researchers' interest and the constant improvement in the therapeutic methods used for brain lesions are fueled by the following:

- The special nature of brain tissue. Healthy, adjacent brain tissue is often affected by the mass effect, hypoxia or ischemia due to the presence of tumors and can react to toxic agents during treatment.
- The repercussions of treatment on the target. Chemotherapy can cause decreased tissue sensitivity and responsiveness to radiotherapy.

The effects of SRS are of two types:

- One is therapeutic efficacy, which is usually documented by images of tumor stability (no progression), a decrease in tumor volume or vascular changes in or around the lesion (obliteration, appearance of black holes).
- The other is observed on images of perilesional abnormalities. This effect comprises a certain number of changes around the target lesions. These changes depend on various factors, such as the administered dose and the tumor's volume and histological type. This effect is often associated with a blood-brain barrier abnormality that causes the release of vasoactive substances. A rigorous clinical and diagnostic follow-up (high-resolution imaging) should be done for this type of lesion [Lunsford et al., 1998].

The adverse effects and complications of SRS can be immediate or late, temporary or permanent, acute or chronic [Werner-Wasik et al., 1999]. The first cases of late brain tissue necrosis were reported by Fisher seven years after the treatment of scalp cancer [Fisher and Holfelder, 1930].

The acute complications (occurring within 24 hours after SRS) include headaches, pain at the points of attachment of the stereotactic frame, and weakness of the limbs. Other, later complications can occur, such as edema (sometimes of acute onset), hemorrhage, and necrosis.

Gamma knife SRS is usually used to treat tumors less than 4 cm in diameter (approximately 13.5 cm^3 in volume). Larger tumors are seldom treated because of the expectation that increasing the target volume will increase toxicity. In a study by Linzer, which involved 35 patients with tumors with a volume greater than 13.5 cm^3 that were treated by gamma knife SRS, only three subjects developed symptoms of acute toxicity. Furthermore, MRI revealed nine cases of necrosis, including three with clinical progression of symptoms. However, no relationship between the prescribed dose and necrosis was found. The authors conclude that the observed level of toxicity (acute and chronic complications) in individuals with large tumors greater than 4 cm in diameter (volume greater than 13.5 cm^3) is acceptable [Linzer et al., 1998].

A histological examination of the areas of necrosis observed after SRS in individuals with AVMs indicated that the lesions were most often due to the destruction (perforation) of vessels, which was attributed to a loss of collagen, fibrinoid necrosis and thrombosis [Yamamoto et al., 1995]. In general, gray matter is affected less than white matter. There was a report of increased vascular patency [Pennybacker and Russell, 1948].

Two researchers classified the various adverse effects according to their time to onset [Sheline and Tyrell, 1984]:

a) Acute reactions occurring during the treatment period. The most likely hypothesis is

that they are due to edema. They do not occur when the radiation doses are fractionated and are less than 2 Gy. MRI images reveal the formation of edema [Guo et al., 1993].

b) Early reactions occurring a few weeks to a few months after radiotherapy.

c) Late reactions occurring several years after radiotherapy. It is generally agreed that the severity of late reactions is not only associated with the administered dose, but also with the volume of irradiated tissue. It was very quickly realized that the lesions were associated with the volume of irradiated tissue. It was observed that a certain dose could be harmless for small tumors but caused necrosis in the case of larger tumors. Fractionating the dose in conventional radiotherapy reduces the incidence of these adverse effects. Since the advent of single-dose treatment, the administered dose/tumor volume ratio has become the most important risk factor.

With regard to late reactions, Radanowicz-Hartman et al. observed, in a case study, vascular obliteration on angiograms several years (6.5 years) after gamma knife treatment [Radanowicz-Hartmann et al., 1998]. Other authors report the occurrence of such lesions 5 to 10 years after SRS [Kihlstrom et al., 1997; Yamamoto et al., 1995]. These authors feel that a long-term follow-up is necessary, even if the therapeutic objective has been achieved [Flickinger et al., 1999; Kihlstrom and Karlsson 1999; Kobayashi et al., 1994; Yamamoto et al., 1995].

The high rate of complications following radiosurgical treatment reported by various facilities worldwide has prompted a reassessment of the indications for SRS and of SRS treatment methods [Foote et al., 1999]. For example, at the Mayo Clinic (United-States), it was decided to reduce the radiation doses administered for certain conditions and to no longer treat large tumors by SRS [Foote et al., 1995].

The RTOG conducted a phase I and II study of the treatment of recurrent tumors (previously irradiated brain tumors and brain metastases) [Shaw et al., 1996]. The results revealed two predictive variables for the occurrence of signs of toxicity associated with the treatment (morbidity due to the treatment): a tumor diameter greater than 3 cm and tumor homogeneity. Furthermore, the results showed that the progression of more than 80% of the tumors was controlled and that SRS was well tolerated, despite the occurrence of a few adverse effects (nausea and vomiting in the subjects with tumors near the fourth ventricle) [Shaw et al., 1996].

The adverse effects of SRS may be due to many different factors, including:

- The number of isocentres
- The dose absorbed by healthy tissues
- The volume of the tumor

Apart from dose distribution heterogeneity, other factors that are still not clearly understood may play a role in the occurrence of complications [Karlsson et al., 1999; Leksell, 1971a]. In addition, the frequency of secondary lesions varies according to the type of pathology [Niemela et al., 1996; Kihlstrom et al., 1993; Lindquist et al., 1993]. The occurrence of cysts is a potential late complication that can cause functional disorders, such as seizures.

The use of markers, such as fluorodeoxyglucose, in conjunction with positron-emission tomography has been recommended for monitoring SRS-treated brain metastases and detecting complications. This approach does, however, have certain limitations, and the volume of the tumor must increase by at least 25% in order for one to be able to make a definitive diagnosis of recurrence.

In summary, here are the radiosurgery-related factors that play a role in the occurrence of complications, healthy, adjacent tis-

sue being the main area affected by adverse effects [Kramer, 1968]:

- The total dose: The incidence and severity of adverse effects increases with the administered dose.
- The total-dose administration time: The faster the dose is administered, the greater the risk.
- The irradiation volume: The probability of lesions occurring increases as the target volume increases.
- Tissue oxygenation: Rays have a greater effect on well-oxygenated tissues.

The following steps are necessary for optimal utilization of the technique and for minimizing the adverse effects:

a) *Rigorous planning.*

b) A dose appropriate to the target volume.

c) A good knowledge of the likelihood of adverse effects, especially late lesions and the more frequent complications after the linear accelerator treatment of pituitary adenomas [Yamamoto et al., 1995; Ganz et al., 1993].

d) Taking the severity of prior hemorrhage into consideration, this in addition to a long-term follow-up in patients with AVMs [Flickinger et al., 1999].

6 SAFETY AND PREVENTIVE MEASURES

The experience with SRS acquired at the Karolinska Institute (gamma knife) argues in favour of using this technology solely for small tumors and indicates that one could attenuate or even avoid certain adverse effects with the new neuroimaging techniques [Lindquist et al., 1991]. A follow-up over several years is often necessary.

Technologies such as CT, MRI, and positron-emission tomography can be used to monitor changes and to remedy the adverse effects due to SRS [Levivier et al., 2000; Curran et al., 1987; Tsuruda et al., 1987; Patronas et al., 1982; Deck, 1980].

It is generally agreed that the radiation dose is what determines the risk of complications the most [Flickinger et al., 1998; Lax and Karlsson, 1996]. Dose determination depends on the following two factors:

- The technical ability to reach the entire target volume.
- The instrument's performance.

Many studies have examined the determination of the effective dose (optimal dose above which there is a risk) [Somigliana et al., 1999; Nizin, 1998]. An experimental study conducted by Ishikawa et al. confirmed the hypothesis that there is a dependent dose-effect relationship with the use of the gamma knife (with doses greater than 50 Gy) [Ishikawa et al., 1999]. In another study, Miller et al. observed that, for VSs, radiosurgical doses less than or equal to 16 Gy resulted in a reduction in the risk of permanent facial paralysis [Miller et al., 1999]. However, other experimental and clinical studies are needed to determine the optimal radiation doses in the treatment of functional disorders of cerebral origin.

The risk of complications varies according to the type of pathology treated. In France (Lyon), SRS (linear accelerator) is used for pituitary adenomas only if they are less than 2 cm in diameter and are located at a certain distance from the optic chiasma.

In order for SRS to be effective and target lesions precisely, a rigorous quality control program is necessary. At the Joint Center for Radiation Therapy in Boston [Tsai et al., 1991], a program has been developed for the linear accelerator that includes the following measures:

a) Checking that the instrument is working properly by performing tests and checking the stereotactic positioning system.

b) A protocol for cross-checking the treatment planning process.

c) A quality assurance checklist for the treatment delivery procedure. Since SRS instruments, particularly linear accelerators, are not immune to radiation leaks, special measures are recommended [Stern, 1999].

Like any other treatment that uses radiation sources, SRS requires the preventive measures inherent in radiotherapy (Appendix F). Setting up an SRS unit involves applying and maintaining the necessary radiation protection standards (structures, patients and personnel) and establishing control measures—in some cases, specific—for certain instruments. While the preparation and adjustment protocol may be uniform for the gamma knife, it is not so for linear accelerators, especially those that are not neurosurgery-dedicated. As a general rule, there are four control steps:

- Checking and adjusting the instrument.
- Checking that the patient is properly prepared.
- Locating the target by imaging (MRI, CT, etc.) and transferring the images.
- Determining the ballistics and dosimetry.

For these measures, each treatment team member must have specific skills and qualifications. Patient management depends on several factors, including the multidisciplinary makeup of the technical/medical team. Apart from the personnel normally present during radiotherapy, a neurosurgeon and a neuroradiologist should participate in the treatment. It should be noted that the stereotactic frame should be attached by qualified personnel.

Here are a few of the general measures required in SRS:

- Ensure that the instrument complies with international quality control standards for medical electron accelerators: International Electrotechnical Commission standards (Appendix F).
- Apply the recommendations of the American Society for Therapeutic Radiology and Oncology and the American Association of Neurological Surgeons (task forces) [Consensus statement on stereotactic radiosurgery quality improvement, 1994]. These recommendations spell out verification measures for patient selection, compliance with technical standards and the training of personnel in charge of training.

7 CURRENT DATA AND INCIDENCE OF TARGET PATHOLOGIES IN QUÉBEC

The results of the various prospective studies conducted by CEDIT [Courtay, 1998] (France) and the Oregon Health Resources Commission [OHRC, 1997] (USA) indicate that the number of patients who will eventually need SRS is approximately 40 (minimum) per one million population per year. Extrapolating this figure only to Québec gives approximately 300 cases per year (1,200 for all of Canada). This estimate concerns only three indications (metastases, schwannomas and vascular malformations). Other authors arrive at much higher figures in the order of 180 cases per one million population per year (or 1,260 in Québec). In our opinion, and based on data from the *Fichier des tumeurs du Québec* and from Canadian Cancer Statistics 2000, a more cautious calculation would bring the number of eligible cases in Québec to 400.

The number of brain tumors in Québec is steadily on the rise (Table 8; Table G.3 in appendix G). Based on the National Cancer Institute of Canada's calculations for the year 2000, the number of cancerous brain tumors diagnosed in Canada is estimated at 1,300, with 660 in Québec (National Cancer Institute of Canada, Canadian Cancer Statistics 2000). It should be noted that these figures concern only primary tumors.

One of the other indications for SRS is AVMs, of which there are between 100 and 120 cases per year, according to existing epidemiological data. For the year 1993-1994, AVMs (all grades combined) warranted 82 craniotomies in Québec.

Based on current data (Tables G.1A and G.1B in Appendix G) and estimates presented by some authors (Tables G.4 and G.5 in Appendix G), the number of cases of brain metastasis potentially eligible for SRS is between 400 and 1,200 per year.

In Québec, the use of SRS is limited to the utilization of the linear accelerator (McGill University Health Centre and *Centre hospitalier universitaire de Montréal*). Most of the indications for which SRS could be useful are currently treated by conventional means, including neurosurgery, standard radiotherapy and chemotherapy in various combinations.

TABLE 8

Number of brain tumors, both sexes combined, Québec, 1992-1996

ICD-9[1]	1992	1993	1994	1995	1996
02191.0 to 02192.9[2] + 02194.3 + 02194.4	521	553	626	620	620[2]

1. ICD-9: International Classification of Diseases (see Table G3 in Appendix G).
2. ICD 191-192: 612 new cases reported in 1996 (283 in women and 329 in men).
Source: *Fichier des tumeurs du Québec*, 1996.

8 COST OF SRS

8.1 COST OF SRS BY INSTRUMENT

Among the instruments considered are the gamma knife (manufactured by only one company) and linear accelerators, which can be modified. A modified linear accelerator can be adapted (by the addition of accessories) or dedicated (exclusive use in SRS).

In addition to the data on the gamma knife provided by the manufacturer (Tables H.3 and H.5 in Appendix H), we chose the economic analysis reports by the following five authors:

- Epstein [Epstein and Lindquist, 1993] (Tables H.1, H.2, and H.3 in Appendix H).
- Königsmaier [Königsmaier et al., 1998] (Tables 9 and 10, and Table H.3 in Appendix H).
- *Centre hospitalier universitaire de Sherbrooke* [CHUS, 2000] (Tables H.3 and H.4 in Appendix H).
- *Agence nationale d'accréditation et d'évaluation en santé* [ANAES, 2000].
- The Medicare Services Advisory Committee, an Australian agency [MSAC, 2001].

Making no claim to be *the* model to be followed for reimbursing the costs inherent in SRS, the Austrian study conducted by Königsmaier is nonetheless useful for comparing the costs directly associated with each of the instruments used. Their study was based on the following three main considerations:

- A new facility.
- The costs directly associated with the use of the equipment.
- The principle of optimal use of the technology.

The economic data compared are the investment cost (acquisition and renovations), the operating costs, and the professional fees.

Based on the results presented by Königsmaier et al., and in light of the data that were valid during the study, the gamma knife is the most expensive of the three instruments in terms of purchase cost. The acquisition cost of a gamma knife, a dedicated linear accelerator and an adapted linear accelerator is $8.36, $4.44 and $3.09 million CDN, respectively. According to the ANAES, and based on an estimate made for a national state health insurance office [Aliès-Patin and Debeugny, 1994], the acquisition cost of a gamma knife in 1994 was 25 million francs. It is not indicated whether this figure includes the renovation costs.

The cost of the personnel who operate and use a gamma knife, a dedicated linear accelerator and an adapted linear accelerator is $314,000, $500,000, and $250,000 CDN, respectively (Table 9). These figures include all of the salaries paid each year for all the SRS treatment teams. These cost estimates are based on the assumption that the permanent team can provide the necessary treatments without it being necessary to hire temporary staff for vacations, sick leave, further training, etc. One should expect a 20% increase in these fees if additional staff are hired for the days when permanent staff are absent [Königsmaier et al., 1998].

TABLE 9

Acquisition and annual operating costs for SRS instruments

	GAMMA KNIFE (CANADIAN DOLLARS)*	DEDICATED LINEAR ACCELERATOR (CANADIAN DOLLARS)	ADAPTED LINEAR ACCELERATOR (CANADIAN DOLLARS)
Cost of instrument	7.05 million	2.86 million	1.51 million
Renovation costs[1]	1.31 million	1.58 million	1.58 million
Total	8.36 million	4.44 million	3.09 million
ANNUAL OPERATING COSTS			
Personnel costs	**314,300**[3]	**500,000**[4]	**250,000**[4]
Physicians[2]	157,143	209,524	104,726
Radiophysicists	95,238	95,238	33,333
Others	61,919	195,238	111,941
Physical resources[5]	**202,190**	**283,143**	**228,973**[6]
Maintenance only[7]	171,429	220,000[8]	197,143[8]
Total	516,490	783,143	478,973

* Based on an exchange rate in effect in 1995 ($1 CDN = 1.05 DM).
1. Renovation costs vary according to the site chosen (e.g., construction or no construction).
2. The medical personnel cost figures are based on physicians' annual salaries.
3. The salaries paid are similar up to 200 patients. Beyond this number, 20% must be added to the basic cost.
4. The salaries paid are similar up to 100 patients. Beyond this number, 20% must be added to the basic cost.
5. These costs were calculated on the basis of optimal equipment utilization and concern water and electricity requirements, cleaning, dosimetry, checking the radiation protection measures, and maintenance. The annual cost of cleaning and radiation protection testing is the same for all three instruments.
6. Calculation based on the use of the instrument for SRS in 50% of cases.
7. This cost does not vary with the number of patients treated.
8. Also includes maintenance of the accessories needed for SRS.
Source: [Königsmaier et al., 1998].

There is no prescribed frequency for replacing cobalt sources, but the treatment time will gradually become longer with the gradual disintegration of these sources, and the utilization cost will increase accordingly. The best time to replace the sources used for each gamma knife could be calculated by means of a cost analysis, but the timing is up to the user. The manufacturer recommends replacing the sources every 7 years, although the calculations presented in the reports by CHUS [CHUS, 2000] and Königsmaier [Königsmaier et al., 1998] are based on periods of 8 and 10 years, respectively.

Königsmaier et al. also estimated the total cost of an SRS treatment according to the equipment used and the annual number of treatments (Table 10).

In their conclusions, the authors of this study consider the gamma knife to be a beneficial technology, if a large number of patients are treated and if optimal use is made of the instrument. Assuming that it is of equal technical performance, the adapted linear accelerator would be more appropriate if fewer patients are to be treated (less than 150). In this report, the cost of a gamma knife treatment ranges from $8,327 to $5,254 CDN for a patient volume ranging from 150 to 250. In Alberta and Ontario, the cost of a linear accelerator treatment in 1996 was estimated, respectively, at $4,000 and $8,000 CDN (even $11,000) [Schneider and Hailey, 1998].

TABLEAU 10

Total per-patient cost of treatment by instrument

NUMBER OF TREATMENTS	GAMMA KNIFE (CANADIAN DOLLARS)	DEDICATED LINEAR ACCELERATOR (CANADIAN DOLLARS)	ADAPTED LINEAR ACCELERATOR (CANADIAN DOLLARS)
100	12,482 *(10,911)*	12,968 *(10,873)*	8,897 *(7,849)*
150	8,327 *(7,229)*	8,780 *(7,383)*	6,537 *(5,699)*
200	6,249 *(5,463)*	6,536 *(5,488)*	
225	5,836 *(4,998)*	6,265 *(5,147)*	
250	5,254 *(4,500)*	5,649 *(4,644)*	

Notes:

- Based on an exchange rate in effect in 1995 ($1 CDN = 1.05 DM).
- The total cost includes the annual amortization of the acquisition and renovation costs, the interest charges at an annual rate of 6% on the invested capital (respectively, $1,005, $618, and $532 per patient, based on the estimate), the annual operating costs, and the salaries (permanent and extra staff), including the physicians' salaries.
- Based on the assumption that the gamma knife and accelerator have a lifespan of 20 and 10 years, respectively.
- The figures in parentheses are the total per-patient treatment costs for the instrument in question, excluding the physicians' salaries.

Source: [Königsmaier et al., 1998].

The Australian agency MSAC compared only the per-treatment costs of the instruments without taking the operating costs into account. In the proposed scenarios, the gamma knife is 1.7 to 2.9 times more expensive than the adapted linear accelerator [MSAC, 2001]. This can be explained by the fact that the cost of a gamma knife accounts for approximately 60% of the total per-treatment cost. In addition, these calculations are based on the assumption that the lifespan of a gamma knife is between 10 and 14 years, that of a linear accelerator between 6 and 14 years, and that the cobalt source is replaced every 5 to 7 years.

At CHUS [2000], it is estimated that each gamma knife treatment costs an average of $4,054 CDN during the first five years of the instrument's life (calculation based on 167 patients treated annually) and $3,027 after the fifth year (cruising mode) (Table 4 in Appendix H). However, these estimates do not include the physicians' professional fees (in Québec, physicians are paid on a fee-for-service basis, with the fee ranging from $540 to $810 CDN, depending on whether an external or interstitial technique is used to localize the lesion), the amortization of the renovation costs, the interest on the invested capital and a few other cost components, such as energy. If these items are taken into account, the per-treatment cost would slightly exceed Königsmaier et al.' cost estimate.

We wish to make the following two comments about these estimates:

- On the one hand, although it is relatively easy to determine the costs (purchase, operating and maintenance) associated with

the gamma knife (a single manufacturer), it is not so for linear accelerators, especially dedicated linear accelerators (several manufacturers and many different models).

- On the other hand, because of the technological evolution of SRS in general and of dedicated linear accelerators in particular, any comparison between the new models of gamma knife and the latest dedicated linear accelerators should be made with caution.

Tables H.3, H.4, and H.5 in Appendix H show the purchase, operating and maintenance costs for the different instruments used in SRS found in the four reports consulted in this regard. These figures show the price differential between the gamma knife and linear accelerators, depending on the authors, and the differences in operating costs for the gamma knife according to the number or procedures performed and to whether or not the investment costs are included.

8.2 COMPARISON BETWEEN SRS AND NEUROSURGERY

The economic studies comparing SRS and microsurgery have essentially concerned VSs and brain metastases, and all of them arrive at the following conclusions:

- Upon comparing the costs of the treatments (surgical excision and SRS), two main differences are noted with respect to the following:
  - Hospital costs (including hospitalization and treatment): Surgery is 1.5 times more expensive than SRS.
  - The fees and salaries of the professionals (surgeons, anesthesiologists, physicists, etc.): They are 1.5 times higher for microsurgery.

Estimates based on the diagnostic-related groups system put the cost of a craniotomy, in the absence of complications, at $5,366 in Manitoba [Jacobsen et al., 1999], $7,273.52 in Alberta [Jacobs and Bachinsky, 1997] and $8,256 in Québec [*Ministère de la Santé et des Services sociaux*, 2000]. The observed differences are due to the duration of hospitalization (e.g., 6.3 days in Manitoba and 9 days in Québec). The study conducted in the United Kingdom by Charny confirms these results: SRS costs half as much as surgical treatment [Charny, 2000].

- Postoperative complications are one of the important variables revealed in that assessment [Charny, 2000], as they are partly responsible for the differences in the cost of surgery for the above-mentioned indications. These complications include, among others:
  - Hemorrhage
  - Infections
  - Facial nerve injury, which can result in facial paralysis and require surgical reintervention.
  - The postoperative formation of a cerebrospinal fistula (25% of cases) requiring reintervention and thus prolonging the hospital stay.

Table 11 recaps the main elements responsible for the differences observed between SRS and microsurgery in terms of the cost of treatment.

TABLE 11

Comparison between SRS and microsurgery

TYPE OF TREATMENT	ADVANTAGES	LIMITATIONS
SRS	• **Short hospital stay (maximum of 12 hours).*** • Noninvasive procedure. • **No general anesthesia.** • **Few or no complications.** • Psychosocial sequelae: SRS is better accepted by patients and permits a better quality of life. • **Very short convalescence period.**	• Risk of hemorrhage after obliterating AVMs. • Length of time between SRS and a decrease in hormone secretion. • Not possible to visually examine the lesions (except by imaging).
Microsurgery	• Sometimes has a rapid effect on tumor compression and hormone secretion. Possible to stop hemorrhage immediately in cases of AVMs. • Effective for large lesions and against certain specific lesions. No edema.	• **Unknowns in any surgical intervention**: risk of infection, problems associated with general anesthesia. • **Mean hospital stay of 8.9 days in Québec†.** • Risks associated with neurosurgery if the tumor is near a critical structure or in a hard-to-reach location. • Some patients find the psychosocial sequelae difficult to accept. • **Convalescence relatively long, even if there are no complications.**

* Note: The **boldfaced** items are, together with the cost of the instrument and the operating costs, those that contribute to making SRS more efficient than microsurgery.
† Mean duration of stay (source: *Ministère de la santé et des services sociaux*).

8.3 COST-EFFECTIVENESS

As we have seen, there have been no rigorously designed studies (randomization, validation) comparing the different instruments used for the same indications. The studies that have been carried out concern different indications, different stages of evolution, or treatment following treatment failure. Furthermore, the evaluation of the images obtained before and after the treatments always depended on the technology and software used.

The only study involving a cost-effectiveness analysis was that by Rutigliano et al., whose objective was to compare gamma knife SRS and surgery for solitary brain metastatic tumors [Rutigliano et al., 1995]. It was an evaluation based on the results of studies conducted between 1974 and 1994 that met strict inclusion criteria. The researchers chose three studies on neurosurgery and one on gamma knife SRS. The costs were estimated from a public insurance plan perspective (cost reimbursed by Medicare in 1992).

When there are no complications, the cost of the complete management of a patient is about $20,209 and $27,587 US, respectively, depending on whether SRS or surgical excision is performed (Table 12). The per-patient cost of treating the complications of SRS and surgery is at least $2,534 and $2,874 US, respectively. Thus, if this cost is included, the total cost of SRS and surgery increases to $22,743 and $30,461 US, respectively.

TABLE 12

Cost estimates (in US dollars) by type of procedure

	RADIOSURGERY (GAMMA KNIFE)	SURGERY
Patient preparation	1,118	1,118
Hospital costs	10,680[1]	16,710[2]
Fees for medical personnel	2,015[3]	3,363[4]
Postoperative care	6,396	6,396
Total	20,209	27,587

1. Includes the hospitalization costs and the cost of the procedure ($9,787 US).
2. For a stay following partial tumor resection.
3. Fees for the SRS personnel.
4. Fees for the surgical personnel (surgeon and anesthesiologist).
Source: Estimates based on Medicare data published in 1992 [Rutigliano et al., 1995].

The mean duration of survival in patients treated with a combination of surgery and radiotherapy, with SRS and with fractionated radiotherapy alone is 11.37, 11, and 4.76 months, respectively.

As for the cost-effectiveness analysis, the parameter considered by the authors was prolongation of survival, expressed as the number of life-years gained following treatment (mean survival expressed in months and divided by 12). This number is 0.948 for neurosurgery plus radiotherapy, 0.917 in the case of SRS, and 0.397 for radiotherapy alone.

The cost-effectiveness analysis (total cost divided by the number of life-years gained following treatment) therefore shows that gamma knife SRS is more efficient than surgery ($24,811 and $32,149 US, respectively).

However, it should be noted that these results were calculated from four different studies, that the surgical treatments were administered by teams with different makeups, and that the primary sites of the metastases were fairly different (lung, melanoma, etc.).

8.4 CONCLUSION

Estimate of the cost of treatment

- Excluding physicians' fees, the cost of using a gamma knife can be estimated at approximately $4,500 CDN per patient if 250 patients are treated each year. If the comparison involves the same number of treated patients, each gamma knife treatment would cost slightly less than if a dedicated linear accelerator were used (assuming that the instruments' lifespan is 20 and 10 years, respectively) and would be more expensive than treatment by means of an adapted linear accelerator. It should be noted, however, that if the use of an adapted linear accelerator is shared between radiotherapy and radiosurgery, the number of cases that could be treated by radiosurgery at each facility would reach a ceiling.
- The number of patients treated is an important variable in determining the average cost per treatment, since this cost (excluding physicians' fees) can drop from

$11,000 to $4,500 CDN as the number of treatments performed with the gamma knife and dedicated linear accelerator increases from 100 to 250. However, the optimal treatment capacity depends on the amount of time it takes to reach this capacity and the number of truly eligible cases in the population.

Assessment of the economic impacts

- According to the CHUS evaluation, the acquisition and renovation costs for a gamma knife are approximately $6.44 million. A dedicated linear accelerator would cost about one half this amount, but its operating costs (physical and human resources) would be 50% higher. It follows that the total cost, including amortization of the instruments, the radiation sources, and the renovations, are approximately the same. As for an adapted linear accelerator, its total cost is 15 to 30% less than that of a gamma knife, given an annual treatment volume of between 175 and 100. All of these figures are based on the purchase of new instruments.
- Assuming that 250 patients are treated annually, the operating cost (excluding physicians' fees) for each gamma knife would be $1.125 million CDN. By comparison, the recurrent costs for operating a dedicated linear accelerator and two adapted linear accelerators (to treat the same number of cases) would be $1.161 million and about $1.5 million, respectively (according to an evaluation done in Austria).
- Based on a cautious determination of the number of cases eligible for radiosurgery, if one wished to treat 300 to 400 cases, the figures above would have to be multiplied by a factor of 1.4 to 1.6. However, this increase would be even greater if, for example, the cases had to be divided between two facilities, since the per-treatment cost increases as the number of cases treated decreases.

Cost-effectiveness

It is difficult to perform a cost-effectiveness analysis because of the following constraints:

- With regard to clinical efficacy, there is no evidence supporting the superiority of one instrument over another. Most studies are not randomized and usually examine various pathologies or clinical conditions, with the result that one cannot apply any standards of comparison.
- In the few studies that have examined the cost of treatment, the latter often depended on the patient's clinical status and on the type of treatment considered (first-line treatment, treatment of recurrences, adjuvant SRS).

In the end, if it is assumed that the treatment is of equal efficacy regardless of the instrument used, the economic comparison criterion would be limited to the per-treatment cost. However, the evaluations do not show a significant difference between the dedicated linear accelerator and the gamma knife, which are more comparable from the standpoint of clinical performance. Lastly, the number of cases that are truly eligible and actually treated is a crucial efficiency factor.

9 DISCUSSION

SRS is a relatively "old" technique that has only truly taken off in the past 10 to 15 years. The interest in this type of treatment is due to the following two factors:

- The desire on the part of therapists to provide the most appropriate and therefore the most effective treatment possible to patients with certain conditions.
- The emergence of a new area of expertise, stereotactic radioneurosurgery.

This second element is the source of opposing positions and even debates regarding the analysis of study results. Such a clash of opinions also occurs among radiation therapists and neurosurgeons, these specialists each having well-established expertise in their respective fields of practice. The question of the appropriateness of this therapeutic area is often raised in publications and comments from both sides.

What seems essential to consider when issuing recommendations is the specialists' approach to choosing between the dedicated linear accelerator and the gamma knife. Given the existing data, the cyclotron, linear accelerator or adapted linear accelerator can only be subjected to a comparative evaluation if the debate is not limited to SRS as currently defined. This issue should be dealt with in the more general framework of treating tumors with radiation (we will intentionally not use the term radiotherapy or radiation therapy so as to include SRS under this heading).

Internationally, the recommendations of the various assessment agencies depend, to a large extent, on the context and vantage points in or from which SRS is implemented. However, most assessment agencies do, in their respective reports (AHFMR in Alberta [Schneider et al., 1998], *Agencia de Evaluación de Tecnologías Sanitarias* in Spain [AETS, 1997], Oregon Health Resources Commission in Oregon, [OHRC, 1997], *Agence nationale d'accréditation et d'évaluation en santé* in France [ANAES, 2000] and Medicare Services Advisory Committee in Australia [MSAC, 2001]), recognize the specific nature of SRS activity and stress the fact that it is difficult to state whether one technique is superior to another. This inability to do so is due essentially to the fact that the instruments are used for different purposes, to the disparity in the treatment processes, to the diversity of the pathologies treated, and especially to the lack of comparative studies of the efficacy of these techniques. In addition, given the lack of valid cost-effectiveness analyses, the existing economic data only provide an indication. Even in this context, and as expressed so well by the ANAES, "the results should be interpreted with caution because of the difficulty in transposing foreign data" (free translation).

It should be noted that these agencies (apart from Alberta's AHFMR and Australia's MSAC) are in countries where both technologies are available.

Two organizations do not arrive at the same recommendations. In its conclusions, CEDIT "does not see any decisive arguments for recommending the acquisition of a gamma knife, which is much more expensive than a linear accelerator" (free translation), and MSAC states that "[s]ince there is currently insufficient evidence on comparative safety, effectiveness and cost-effectiveness pertaining to gamma knife radiosurgery, [it] recommended that additional public funding should not be supported...for this procedure."

To better interpret these conclusions, one must take into consideration the following two points, which weighed in heavily when these recommendations were made:

- **In the case of CEDIT:**
  - The context: The CEDIT report was published in 1997, three years before

the ANAES report, in response to a specific request and within the framework of a project for the acquisition of a gamma knife by *Assistance Publique – Hôpitaux de Paris*. Furthermore, it was a project aimed at acquiring a second instrument of this type in France (in addition to the one already in use in Marseille).

- The "comparative" analysis: This analysis not only concerns SRS, but was performed from a broader perspective, as it examines acquiring the means for providing irradiation treatment. While recognizing that "no argument can be used to state that either of the technologies used in SRS (gamma knife or linear accelerator) is superior to the other" (free translation), CEDIT does admit that "the quality assurance procedures are more complex" (free translation) for the linear accelerator and that "the relative ease of use and robustness argue in favour of the gamma knife" (free translation). Furthermore, the essential element on which this recommendation is based is "mainly the fact that the instrument (gamma knife) is limited to the treatment of brain lesions" (free translation).

- **In the case of MSAC:**
  - The context: MSAC assessed the gamma knife and the benefit of purchasing such an instrument in light of the Australian context, in response to a request from the Australian Ministry of Health. Eight linear accelerators, which are adapted for SRS, are in operation in Australia.
  - The "comparative" analysis: a) The comparison mainly concerns the adapted linear accelerator and the gamma knife, and the assessment concerns only three indications (AVMs, brain metastases, and VSs); and b) the calculation scenarios for the per-treatment equipment cost are based on different comparison assumptions than those found in the rare published study reports on this topic (the instrument's lifespan, the frequency of cobalt source replacement).
  - The conclusion: MSAC recognizes that "[r]adiosurgery may be an effective treatment for selected groups of patients with arteriovenous malformations and acoustic neuroma, for example those patients with surgically inaccessible lesions or those with comorbidities which preclude surgical intervention" and that "[e]vidence does not indicate a difference in outcomes for patients treated with gamma knife or LINAC radiosurgery". This latter statement is not corroborated by the many publications, which usually concern the use of different instruments for other pathologies, with the result that the instruments cannot be compared in terms of efficacy.

In its conclusions, the ANAES adds that there should be "at least one centre using a gamma knife and at least one using a dedicated linac" and that "dedicated centres should collaborate in clinical research so that a comparative assessment of the two technologies can be made" (free translation).

These various analyses are based on the priority choices that policymakers have to make not only with regard to health care, given the population's needs, the development of services suited to these needs, and the economic constraints, but also with regard to clinical and basic health research. The recommendations that might ensue from this assessment should take these more general concerns into account and be based on the best scientific data possible, which we attempted to synthesize in this report, and which other assessment agencies that have produced reports on this subject have attempted to do in theirs.

10 CONCLUSION

An analysis of the data revealed three levels of assessment: the role of SRS, the efficacy of this treatment modality in light of the instrument used, and lastly, the choice of a technique appropriate for Québec. Here are the specific conclusions concerning each of these aspects.

Stereotactic radiosurgery

- SRS is a treatment modality generally recognized as safe.
- The efficacy of SRS has been established for a certain number of indications, including brain metastases, AVMs, as an alternative to conventional surgery in cases of interventional difficulties, and in the avoidance of the complications of the standard treatments in cases of meningioma and VSs. SRS is a promising approach in the treatment of pituitary adenomas, certain skull base tumors, and specific functional disorders.
- For certain types of brain lesions and certain clinical conditions, SRS costs less than surgery.
- Given the evolution of the technologies and the costs associated with SRS, the instruments that might best meet the efficacy and safety criteria are the dedicated linear accelerator and the gamma knife.
- The use of an adapted linear accelerator is possible but limited in cases of lesions in very close proximity to sensitive structures, since the manipulations required to adapt the equipment in order to perform SRS can be a source of imprecision when focussing the beams. Furthermore, the need to perform quality control before each treatment lengthens the treatment time.
- Presently, SRS facilities are clearly needed in Québec. If we consider all the lesions eligible for SRS on the basis of the existing data and estimates, more than 300 patients could qualify for SRS.

Therapeutic efficacy by instrument

- Even if, in theory, the gamma knife and dedicated linear accelerator are both more suitable for the different indications for SRS, technological developments in the specific area of SRS (especially in the case of the dedicated linear accelerator) and the lack of randomized, controlled trials concerning a given indication do not permit us to conclude that either of these instruments is superior to the other from the standpoint of efficacy. However, the degree of precision offered by the gamma knife permits the treatment of lesions that are no more than 2 mm in size and which touch vital structures, such as the cranial nerves, optic chiasma and brainstem, without (theoretically) causing any injury to healthy tissues.

SRS in the Québec context

Given the current knowledge about the clinical, economic, technical and epidemiological aspects and given the need to adequately fulfill the offer of SRS services and to adequately meet research needs, the *Agence d'évaluation des technologies et des modes d'intervention en santé* recommends that a specialized radiosurgery centre with a gamma knife be created at a university hospital. Where this specialized centre will be set up will depend on geographical and/or functional accessibility and well-established service pathways.

The selected institution must have the necessary logistics (structural and professional) needed to perform this type of treatment. The mandatory presence of a multidisciplinary team (neurosurgeon, neuroradiologist, radiation therapist, radiophysicist, paramedical personnel) with an interdisciplinary mode of operation, the need to provide continuous, high-quality patient management, and the need to promote the acquisition of new professional skills clearly warrant creating the centre at a university hospital.

These conclusions are conditional upon the technological evolution of the various types of instruments and the emerging therapies (fractionated stereotactic radiotherapy) at the time when the decision to create a centre providing SRS services is made.

APPENDIX A: TECHNICAL CHARACTERISTICS OF VARIOUS SRS INSTRUMENTS

INSTRUMENT	CYCLOTRON	GAMMA KNIFE	LINEAR ACCELERATOR
Type of rays	Protons, α-rays, etc.	γ-rays	x-rays
Source	Ionization of particles (e.g., hydrogen)	Cobalt 60	Bombardment of a tungsten target
Energy/particle	150 to 235 MeV	1.17 to 1.33 MeV	1 to 25 MeV
Precision	0.1 mm	0.2 mm	Down to 0.2 mm*
Configuration	Single fixed source Patient moves	Multiples fixed sources Patient stationary	Fixed source Patient stationary

* Precision varies according to the model.

APPENDIX B: MAIN DIFFERENCES BETWEEN SRS INSTRUMENTS

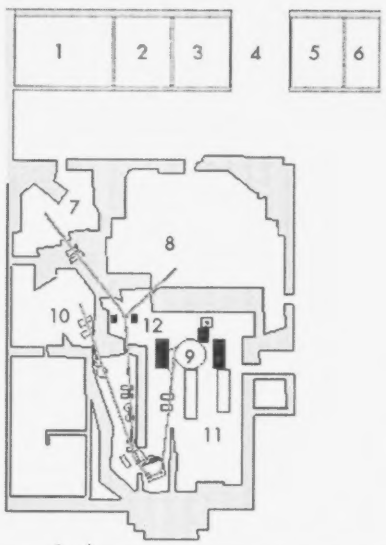
INSTRUMENT	CYCLOTRON	ADAPTED LINEAR ACCELERATOR (SHARED)	DEDICATED LINEAR ACCELERATOR	GAMMA KNIFE
Characteristics and properties	▪ Used in many areas of research. ▪ Prototype manufacture.	▪ Linear accelerator to which accessories are added (e.g., collimator and software for use in SRS).	▪ Linear accelerator manufactured exclusively for SRS. ▪ Properties of the multileaf collimator.	▪ Is intended exclusively for SRS.
Advantages	▪ Very high level of precision.	▪ Purchase cost.	▪ Purchase cost. ▪ Wide range of collimators. ▪ Ability to treat irregular lesions.	▪ Radiation protection not very expensive. ▪ Stability of precision.
Drawbacks	▪ Elaborate structure and equipment. ▪ High cost.	▪ Radiation protection expensive. ▪ Adjustment can be a source of imprecision when targetting the beams. ▪ Length of the procedure (quality control before each treatment).	▪ Radiation protection expensive. ▪ Length of the procedure (quality control before each treatment).	▪ High purchase cost. ▪ Replacing the cobalt sources (every 8 years).

APPENDIX C : PROTON THERAPY

FIGURE C.1

Proton therapy unit

1) Salle de mesure
2) Salle de dosimètrie
3) Bureau médical
4) Entrée principale
5) Secrétariat
6) Salle d'attente
7) Salle de traitement N° 1
8) Salle de traitement N° 2
9) Synchrocyclotron
10) Future salle de traitement N° 3
11) Salle du synchrocyclotron
12) Aiguillage

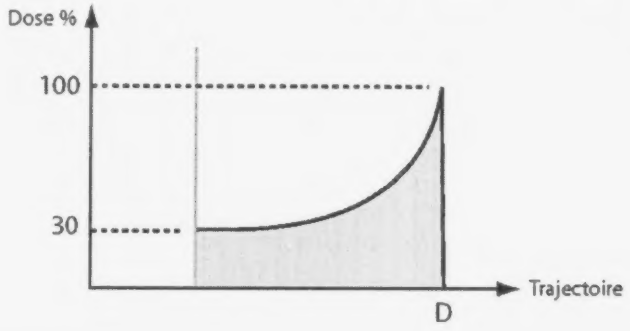


Source: *Centre de protonthérapie d'Orsay*, France (reproduction authorized)

FIGURE C.2

Diagram of Bragg's peak

This diagram shows the dose distribution along the proton's trajectory. The delivered dose increases as the particles' energy decreases.

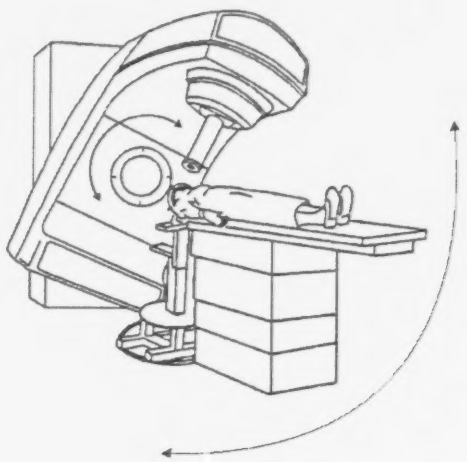


Source: *Centre de protonthérapie d'Orsay*, France (reproduction authorized).

APPENDIX D: THE LINEAR ACCELERATOR

FIGURE D.1

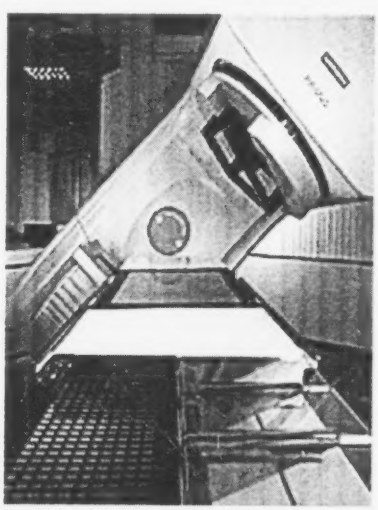
Diagram of one type of linear accelerator (both source and patient move)



Source: Siemens Canada Limited (reproduction authorized)

FIGURE D.2

Linear accelerator with integrated, 3-dimensional multileaf collimator (PRIMUS linear®)

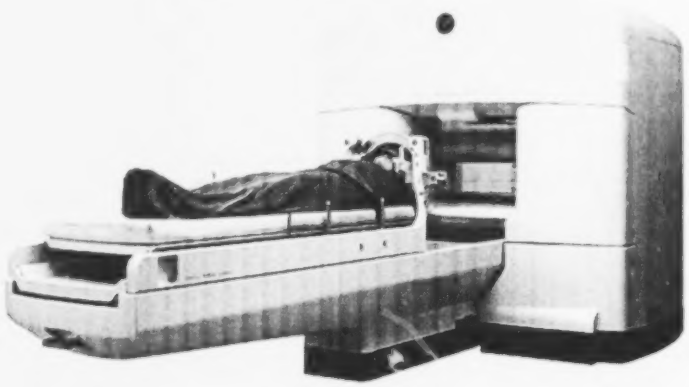


Source: Siemens Canada Limited (reproduction authorized)

APPENDIX E: THE GAMMA KNIFE

FIGURE E.1

Gamma Knife Instrument (Leksell Gamma Knife ®)



Source: Elekta Instrument AB (reproduction authorized)

APPENDIX F: STATUTES AND REGULATIONS CONCERNING RADIOSURGERY

Under the *Food and Drugs Act* and the *Radiation Emitting Devices Act*, Health Canada regulates the sale of medical equipment (e.g., x-ray machines and drugs containing radioisotopes) and the sale of medical particle accelerators in order to ensure operator and patient safety when the equipment, drugs and accelerators are used according to instructions and to ensure their efficacy in view of the objectives.

Under the *Nuclear Safety and Control Act*, the Canadian Nuclear Safety Commission regulates the possession and use of radioactive substances, in particular, the use of radioisotopes in medical equipment and the use of medical particle accelerators that produce nuclear energy.

Presently, the use of medical linear accelerators and of cyclotrons is governed by the *Class II Nuclear Facilities and Prescribed Equipment Regulations* (if the instrument produces more than 50 MeV, it falls under the *Class I Nuclear Facilities Regulations*). As for gamma knife accelerators, they are governed by the *Nuclear Substances and Radiation Devices Regulations*.

Listed below are the statutes and regulations concerning radiotherapy and radiation protection equipment.

- Federal statutes and regulations
  - *Nuclear Safety and Control Act* (C.S. 1997, c. 9, particularly Section 44)
  - *Nuclear Substances and Radiation Devices Regulations* (SOR/2000-207)
  - *An Act respecting food, drugs, cosmetics and therapeutic devices*, (R.S.C. 1985, c. F-27)
  - *Radiation Emitting Devices Act* (R.S.C. 1985, c. R-1).
- Provincial statutes and regulations
  - *Public Health Protection Act* (R.S.Q., c. P-35)
  - *Environment Quality Act* (R.S.Q., c. Q-2)
  - *An Act respecting occupational health and safety* (R.S.Q., c. S-2.1)
  - *An Act respecting health services and social services (R.S.Q., c. S-4.2)*

- Founded in 1906, the International Electrotechnical Commission (IEC) is a world organization that develops and publishes international standards for everything that has to do with electricity, electronics, and related technologies. The Commission has more than 50 members, including Canada (Standards Council of Canada). The standards are publications based on international consensuses on specific areas of technology, their main purpose being to promote international trade. A consensus is achieved after a mandatory, rigorous process for approving and publishing international standards.

Listed below the international (IEC) and Canadian (CAN/CSA) standards concerning quality control for medical electron accelerators and gamma knives.

- CAN/CSA-22.2 No. 114-M90: Diagnostic Imaging and Radiation Therapy Equipment
- IEC/TR3 61859 (1997-05): Guidelines for radiotherapy treatment rooms design
- IEC 62083 (2000-11): Medical electrical equipment - Requirements for the safety of radiotherapy treatment planning systems
- IEC 60601-2-1 (1998-06): Medical electrical equipment - Part 2-1: Particular requirements for the safety of electron accelerators in the range 1 MeV to 50 MeV
- IEC 60601-2-8 (1999-04) Consolidated Edition: Medical electrical equipment - Part 2-8: Particular requirements for the safety of therapeutic X-ray equipment operating in the range 10 kV to 1 MV
- IEC 60601-2-11 (1997-08)/CAN/CSA-C22.2 No. 601.2.11-92: Particular requirements for the safety of gamma beam therapy equipment
- IEC 60601-2-17 (1989-09)/CAN/CSA-C22.2 n 601.2.17-94: Medical electrical equipment. Part 2: Particular requirements for the safety of remote-controlled automatically-driven gamma-ray afterloading equipment
- IEC 60976 (1989-06): Medical electrical equipment - Medical electron accelerators - Functional performance characteristics
- IEC 60977: Medical electrical equipment - Medical electron accelerators in the range of 1 MeV to 50 MeV - Guidelines for functional performance characteristics
- IEC 61217 (1996-08): Radiotherapy equipment - Coordinates, movements and scales

Note
This list of IEC standards is not exhaustive and does not include those pertaining to individual radiation protection and external dosimetry, which are some of the usual standards used in radiation therapy.

APPENDIX G: FACTUAL INFORMATION

- Studies put the annual incidence of brain metastases at between 2.8 and 12 cases per 100,000 population.
- One or more brain metastases will appear in 25 to 50% of cancer patients.
- Between 5 and 13% of all metastases are brain metastases.
- At autopsy, 50% of brain metastases are of pulmonary or mammary origin.

TABLE G.1A

Overall incidence of brain metastases by type of primary cancer

PRIMARY TUMOR	INCIDENCE (%)	AUTHORS
Lung cancer	10 to 80	Nugent [Nugent et al., 1979]
Breast cancer	20 to 30	Wronski [Wronski et al., 1997]
Melanoma	5 to 21	Delattre [Delattre et al., 1988]
Choriocarcinoma	8.8 to 21.4	Ishizuka [Ishizuka et al., 1983]
Gastrointestinal cancer	1 to 10	Hammoud [Hammoud et al., 1996]
Testicular cancer	2	Guenot [Guenot et al., 1994]
Ovarian cancer	2.2	Bruzzone [Bruzzone et al., 1993]
Endometrial cancer	0.9	Cormio [Cormio et al., 1996]

TABLE G.1B

Estimated number of brain metastases per year by location of the primary tumor

LOCATION OR TYPE OF PRIMARY TUMOR	1996[1]		2000[2]	
	Number of cases	Number of cases of brain metastases*	Number of cases	Number of cases of brain metastases *
Lung	5,404	540	5,950	595
Breast	4,234	846	4,500	900
Melanoma	N.S.	N.S.	550	27
Gastrointestinal tract	2,760	27	2,400	24
Ovary	605	13	720	16
Endometrium	664	6	850	8

1. Source: *Fichier des tumeurs du Québec*, 1996.
2. Source: National Cancer Institute of Canada, Canadian Cancer Statistics 2000.
* Minimum number of cases of brain metastases estimated from established incidence rates.
N.S. Not specified.

TABLE G.2

Karnofsky's Index*

100%	Normal, no complaints, no signs or symptoms of disease.
90%	Able to perform the normal activities of daily living; minor signs or symptoms of disease.
80%	Able to perform the normal activities of daily living with some effort; a few signs or symptoms.
70%	Able to look after him/herself but unable to engage in regular activities or to work.
60%	Requires assistance on occasion but can look after most of his/her personal needs.
50%	Requires continuous assistance and frequent medical care.
40%	Handicapped. Requires assistance and special care.
30%	Severely handicapped. Hospitalization is indicated, although death is not imminent.
20%	Requires hospitalization. Is very sick and requires active supportive therapy.
10%	Moribund. Death process progressing quickly.

* This patient dependency assessment scale is commonly used in palliative care. This version is the one officially issued by France's *Ministère de l'Emploi et de la Solidarité* [*Direction de l'hospitalisation et de l'organisation des soins*, 2001].

TABLE G.3

Number of brain tumors diagnosed in Québec (1992 to 1996)

ICD	1992	1993	1994	1995	1996	TOTAL
02191.0 – Cerebrum, except lobes and ventricles	81	99	104	99	105	488
02191.1 - Frontal lobe	93	96	101	103	100	493
02191.2 - Temporal lobe	63	59	76	65	74	337
02191.3 - Parietal lobe	49	44	43	60	52	248
02191.4 - Occipital lobe	5	8	9	13	4	39
02191.5 - Ventricles	18	10	17	11	14	70
02191.6 - Cerebellum	18	28	20	22	18	106
02191.7 - Brain stem	13	13	10	12	13	61
02191.8 - Other parts of brain	89	105	119	116	133	562
02191.9 - Brain, unspecified	41	45	39	41	48	214
02192.0 - Cranial nerves	4	5	3	1	5	18
02192.1 - Cerebral meninges	17	16	21	28	26	108
02194.3 - Pituitary gland and craniopharyngeal duct	5	5	9	9	4	32
02194.4 - Pineal gland	9	5	4	1	5	24
02198.2 - Skin	7	6	13	9	4	39
02198.3 - Brain and spinal cord	12	22	47	25	15	121
02198.4 - Other parts of nervous system	1	1	2	1	2	7
02234.8 - Other specified sites	3	2	2	3	2	12

Source: *Fichier des tumeurs du Québec*, 1996.

TABLE G.4

Potential indications for SRS

ELIGIBLE PATHOLOGIES	ANNUAL INCIDENCE (IN MILLIONS)	NUMBER OF CASES IN QUÉBEC*	PERCENTAGE OF CASES ELIGIBLE FOR RADIOSURGERY	NUMBER OF CASES ELIGIBLE EACH YEAR FOR RADIOSURGERY
Arteriovenous malformations	17	119	70	83
Meningiomas	16	112	50	56
Neurinomas	10	70	50	35
Craniopharyngiomas	1.5	10	20	2
Pituitary adenomas	12	84	20	17
Solitary metastases	150	1,050	70	735
Multiple metastases	350	2,450	10	245
Gliomas	50	350	10	35
Other tumors	2.5	17.5	10	2
Total				1,266

* This figure was obtained by multiplying the incidence per million population by 7 (the population of Québec is about 7 million).
Source: Internal communication, CHUS.

TABLE G.5

Indications for SRS and estimate of the number of eligible candidates in Québec

INDICATION	ANNUAL INCIDENCE PER MILLION POPULATION	PERCENTAGE OF CASES ELIGIBLE FOR GK SRS	NUMBER OF CASES PER YEAR PER MILLION POPULATION (X 7)	ANNUAL NUMBER OF CASES ELIGIBLE FOR GK SRS IN QUÉBEC
Vascular lesions				
▪ Arteriovenous malformations	19	70	13	91
Benign tumors				
▪ Meningiomas	20	40	8	56
▪ Pituitary tumors	21	20	4	28
▪ Vestibular schwannomas	9.4	63	6	42
Malignant tumors				
▪ Metastases (solitary and multiple)	630	27	170	1,190
▪ Gliomas	40	25	10	70
Other tumors	12	25	3	21
Functional disorders				
▪ Trigeminal neuralgia	43	50	21	147
TOTAL			235	1,645

Source: Leksell Gamma Knife® (according to a written communication to the *Agence d'évaluation des technologies et des modes d'intervention en santé*, December 2000).

APPENDIX H: SRS INSTRUMENT COST DATA

TABLE H.1

Cost of instrument per patient (in Canadian dollars)

ELEMENT	GAMMA KNIFE	15-MEV LINEAR ACCELERATOR
Instrument and installation	$4.07 million	$2.634 million
Lifespan	20 years	10 years
Annual operating cost[1]	$225,600	$278,400
Cost of instrument (basis of 200 patients/year)	$1,128	$1,392

1. Includes the annual capital cost, annual maintenance, and quality control (three times higher for an adapted linear accelerator).
Source: [Epstein and Lindquist, 1993].

TABLE H.2

Total cost per patient and per treatment

ELEMENT	GAMMA KNIFE	15-MEV LINEAR ACCELERATOR
Cost of instrument/patient	$1,128[1]	$1,392
Dosimetry		+ $240[2]
Physicians' fees		+ $120
Engineers' salaries		+ $240
Technicians' salaries		+ $240
Total	$1,128	$2,232

1. Includes all the professional fees.
2. (+) Additional cost per treatment by linear accelerator.
Source: Calculation based on 200 patients treated each year [Epstein and Lindquist, 1993].

TABLE H.3

Acquisition, renovation, and maintenance costs for a gamma knife

INSTRUMENT	EPSTEIN[1]	KÖNIGSMAIER[2]	CHUS*	ELEKTA[3]
YEAR	1992	1995	2000	2000
Instrument and accessories	$3.59 million	$6.77 million	$5.2 million[4]	$5.236 million
Renovations	$480,000	$1,600,000	$1,222,000	$616,000
Annual cost of physical resources and maintenance	$21,600[5]	$202,190	$161,750	$215,600[6]
Number of patients	200	345	240	250
Annual maintenance cost per patient	$108	$586	$674	$862

* Internal communication, CHUS.
1. Based on a 1992 exchange rate ($1 CDN = $1.2 US).
2. Based on a 1995 exchange rate ($1 CDN = 1.05 DM).
3. Manufacturer of the gamma knife. These figures concern Model C.
4. Includes the cobalt-60 sources, which need to be renewed every 8 years, according to a CHUS evaluation.
5. The authors indicate that this is an underestimation. No reference is made to a maintenance contract.
6. The maintenance cost was estimated for a typical year starting the second year and is expressed in constant dollars to make it comparable to the other cost estimates.

Comments

- All of the costs have been converted to Canadian dollars using the exchange rate in effect when the study was conducted (date different from the publication date).
- The model of instrument used is not specified in most of the reports.
- The various estimates do not include the same cost elements, do not use the same amortization periods or do not fall within the same cost analysis framework. Furthermore, the quantities and costs pertaining to human and physical resources vary, mainly because three different countries are represented.
- The substantial differences between the results reported by Epstein [1993] and Königsmaier [1998] can be explained by the publication dates of the two studies and especially by the methodology used by Epstein to estimate the cost per patient. The large difference is due to the annual maintenance costs alone, which are approximately $12,000 CDN in Epstein's report and $171,429 CDN in Königsmaier's report. In these studies, the authors assume that the lifespan of the gamma knife is twice that of the linear accelerator (20 and 10 years, respectively).
- Certain estimates are based on 345 patients treated per year (upper limit) or even 500 (gamma knife), although the normal treatment volume recommended by the manufacturer is 210 patients per year.

TABLE H.4

Total per-patient cost (in Canadian dollars) of treatment by gamma knife according to the CHUS study

NUMBER OF PROCEDURES (YEAR OF USE)	65 (1ST YEAR)[2]	125 (2ND YEAR)	185 (3RD YEAR)	240 (5TH YEAR)
Without renovation costs	8,349	5,510	3,823	3,027
With renovation costs[1]	9,100	5,900	4,774	3,778
With renovation costs and interest on capital[3]	12,095	7,458	5,826	4,557

Comment: All of the costs have been converted to Canadian dollars using the exchange rate in effect when the study was conducted.

Note: The total cost includes staff salaries (excluding physicians' fees), the cost of the procedure, the cost of startup and training (for the first year), the patients' travelling expenses, and the amortization of the sources (reserve for replacing them after 8 years) and gamma knife (over a 20-year period).

1. The renovation costs of $1.22 million are amortized over a period of 25 years.
2. The maintenance for the first year is included in the acquisition cost.
3. The interest charge is the average capital investment (basic amount divided by 2) multiplied by an annual interest rate of 6%, as per the method used by Königsmaier et al.

Source: Internal communication, CHUS.

TABLE H.5

Total per-patient cost of treatment (Elekta® study) in constant Canadian dollars

NUMBER OF PROCEDURES (YEAR OF USE)	150 (1ST YEAR)	173 (2ND YEAR)	228 (4TH YEAR)	250 (5TH YEAR)	250 (8TH YEAR)*
No reserve for replacing sources (initial Elekta estimate)	6,571	6,717	5,869	5,096	8,467
With reserve for replacing sources	7,342	7,505	5,694	5,194	5,194
With reserve and amortization of instrument over 20 years	5,597	5,992	4,546	4,147	4,147
With reserve, amortization over 20 years and interest on capital	6,764	7,007	5,316	4,849	4,849

Based on data provided by ELEKTA (gamma knife, Model C). The amortization period for the instrument per se is 10 years.
* Replacement of cobalt source ($954,800 CDN).

REFERENCES

Adegbite AB, Khan MI, Paine KW, Tan LK. The recurrence of intracranial meningiomas after surgical treatment. J Neurosurg 1983;58(1):51-6.

Agence nationale d'accréditation et d'évaluation en Santé (ANAES). Évaluation clinique et économique de la radiochirurgie intracrânienne en conditions stéréotaxiques. Paris: ANAES, 2000.

Agencia de Evaluación de Tecnologías Sanitarias (AETS). Radiocirugía estereotáctica : indicaciones y situación en España. Madrid: Miniserio de Sanidad y Consumo, Instituto de Salud Carlos III, AETS, 1997.

Al-Mefty O, Fox JL, Smith RR. Petrosal approach for petroclival meningiomas. Neurosurgery 1988;22(3):510-7.

Alexander E 3d., Lindquist C. Special indications: radiosurgery for functional neurosurgery and epilepsy. In: Alexander EI, Lindquist C, Lunsford LD, editors. Stereotactic radiosurgery. New York: McGraw-Hill, 1993, pp. 221-5.

Alexander E 3rd, Loeffler JS. Radiosurgery using a modified linear accelerator. Neurosurg Clin N Am 1992;3(1):167-90.

Alexander E 3rd, Loeffler JS. Radiosurgery for primary malignant brain tumors. Semin Surg Oncol 1998;14(1):43-52.

Alexander E 3rd, Loeffler JS. The case for radiosurgery. Clin Neurosurg 1999;45:32-40.

Alexander E 3rd, Moriarty TM, Davis RB, Wen PY, Fine HA, Black PM, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87(1):34-40.

Aliès-Patin C, Debeugny G. Évaluation du coût d'un traitement par Gamma Unit hors rémunération médicale. Paris: CNAMTS - Division de la nomenclature, 1994.

Amin-Hanjani S, Ogilvy CS, Candia GJ, Lyons S, Chapman PH. Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron. Neurosurgery 1998;42(6):1229-36; discussion 1236-8.

Arita K, Ikawa F, Kurisu K, Sumida M, Harada K, Uozumi T, et al. The relationship between magnetic resonance imaging findings and clinical manifestations of hypothalamic hamartoma. J Neurosurg 1999;91(2):212-20.

Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, et al. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. Int J Radiat Oncol Biol Phys 1996;35(1):27-35.

Barbaro NM, Gutin PH, Wilson CB, Sheline GE, Boldrey EB, Wara WM. Radiation therapy in the treatment of partially resected meningiomas. Neurosurgery 1987;20(4):525-8.

Baxter LR Jr, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 1992;49(9):681-9.

Black PM. Meningiomas. Neurosurgery 1993;32(4):643-57.

Blonder LX, Hodes JE, Ranseen JD, Schmitt FA. Short-term neuropsychological outcome following Gamma Knife radiosurgery for arteriovenous malformations: a preliminary report. Appl Neuropsychol 1999;6(3):181-6.

Boyd TS, Mehta MP. Stereotactic radiosurgery for brain metastases. Oncology (Huntingt) 1999;13(10):1397-409; discussion, 1409-10, 1413.

Breneman JC, Warnick RE, Albright RE Jr, Kukiatinant N, Shaw J, Armin D, et al. Stereotactic radiosurgery for the treatment of brain metastases. Results of a single institution series. Cancer 1997;79(3):551-7.

Bruzzone M, Campora E, Chiara S, Giudici S, Merlini L, Simoni C, et al. Cerebral metastases secondary to ovarian cancer: still an unusual event. Gynecol Oncol 1993;49(1):37-40.

Busse PM. Radiation therapy for meningiomas. In: Schmideck HH, editor. Meningiomas and their surgical management. Philadelphia: Saunders, 1991, pp. 507-18.

Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Stereotactic Radiosurgery. Ottawa: CCOHTA, 1992.

Centre hospitalier universitaire de Sherbrooke. Service de neurochirurgie. La radiochirurgie stéréotaxique intra-crânienne par Gamma au Québec. May 2000.

Chalifoux R, Elisevich K. Effect of ionizing radiation on partial seizures attributable to malignant cerebral tumors. Stereotact Funct Neurosurg 1996-1997;67(3-4):169-82.

Chang SD, Adler JR Jr. Treatment of cranial base meningiomas with linear accelerator radiosurgery. Neurosurgery 1997;41(5):1019-25; discussion 1025-7.

Chang SD, Adler JR Jr, Martin DP. LINAC radiosurgery for cavernous sinus meningiomas. Stereotact Funct Neurosurg 1998a;71(1):43-50.

Chang SD, Levy RP, Adler JR Jr, Martin DP, Krakovitz PR, Steinberg GK. Stereotactic radiosurgery of angiographically occult vascular malformations: 14-year experience. Neurosurgery 1998b;43(2):213-20; discussion 220-1.

Chang SD, Steinberg GK, Levy RP, Marks MP, Frankel KA, Shuster DL, et al. Microsurgical resection of incompletely obliterated intracranial arteriovenous malformations following stereotactic radiosurgery. Neurol Med Chir (Tokyo) 1998c;38(Suppl):200-7.

Charny M. Radiosurgery: the better alternative. Translucy Ltd, December 2, 2000.

Clayton RN, Stewart PM, Shalet SM, Wass JA. Pituitary surgery for acromegaly should be done by specialists. BMJ 1999;319(7210):588-9.

Coffey RJ. Boost Gamma Knife radiosurgery in the treatment of primary glial tumors. Stereotact Funct Neurosurg 1993;61 Suppl 1:59-64.

Coffey RJ, Lunsford LD. The role of stereotactic techniques in the management of craniopharyngiomas. Neurosurg Clin N Am 1990;1(1):161-72.

Colombo F, Francescon P. Clinical linear accelerator radiosurgery. In: Gildenberg PL, Tasker RR, editors. Textbook of stereotactic and functional neurosurgery. New York: McGraw-Hill, 1998, pp. 757-62.

Condra KS, Buatti JM, Mendenhall WM, Friedman WA, Marcus RB Jr, Rhoton AL. Benign meningiomas: primary treatment selection affects survival. Int J Radiat Oncol Biol Phys 1997; 39(2):427-36.

Consensus statement on stereotactic radiosurgery: quality improvement. Neurosurgery 1994;34(1): 193-5.

Cormio G, Lissoni A, Losa G, Zanetta G, Pellegrino A, Mangioni C. Brain metastases from endometrial carcinoma. Gynecol Oncol 1996;61(1):40-3.

Courtay A. Radiochirurgie : conclusions du groupe de travail. Paris, France: Assistance publique - Hôpitaux de Paris, Direction de la politique médicale, 1998.

Curran WJ, Hecht-Leavitt C, Schut L, Zimmerman RA, Nelson DF. Magnetic resonance imaging of cranial radiation lesions. Int J Radiat Oncol Biol Phys 1987;13(7):1093-8.

Davey P. Brain metastases. Curr Probl Cancer 1999;23(2):59-98.

Debus J, Pirzkall A, Schlegel W, Wannenmacher M. [Stereotactic one-time irradiation (radiosurgery). The methods, indications and results]. Strahlenther Onkol 1999;175(2):47-56.

Deck MDF. Imaging techniques in diagnosis of radiation damage to the nervous system. In: Gilbert HA, Kagan AR, editors. Radiation damage to the nervous system. New York: Raven Press, 1980, pp. 107-27.

Degerblad M, Rahn T, Bergstrand G, Thoren M. Long-term results of stereotactic radiosurgery to the pituitary gland in Cushing's disease. Acta Endocrinol (Copenh) 1986;112(3):310-4.

Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. Arch Neurol 1988; 45(7):741-4.

Direction de l'hospitalisation et de l'organisation des soins (Ministère de l'Emploi et de la Solidarité, République française). Complément à la circulaire DH/EO 2 n° 2000-295 du 30 mai 2000 relative à l'hospitalisation à domicile. Bulletin officiel n° 2001-1; SP 3 31 17.

Duma CM, Jacques D, Kopyov OV. The treatment of movement disorders using Gamma Knife stereotactic radiosurgery. Neurosurg Clin N Am 1999;10(2):379-89.

Eastman RC, Gorden P, Roth J. Conventional supervoltage irradiation is an effective treatment for acromegaly. J Clin Endocrinol Metab 1979;48(6):931-40.

Ebersold MJ, Harner SG, Beatty CW, Harper CM Jr, Quast LM. Current results of the retrosigmoid approach to acoustic neurinoma. J Neurosurg 1992;76(6):901-9.

Edmonds MW, Simpson WJ, Meakin JW. External irradiation of the hypophysis for Cushing's disease. Can Med Assoc J 1972;107(9):860-2.

Edwards-Brown MK, Jakacki RI. Imaging the central nervous system effects of radiation and chemotherapy of pediatric tumors. Neuroimaging Clin N Am 1999;9(1):177-93.

Elwes RD, Dunn G, Binnie CD, Polkey CE. Outcome following resective surgery for temporal lobe epilepsy: a prospective follow up study of 102 consecutive cases. J Neurol Neurosurg Psychiatry 1991;54(11):949-52.

Engel J. Outcome with respect to epileptic seizures. In: Engel J, editor. Surgical treatment of the epilepsies. New York: Raven Press, 1993, pp. 609-22.

Engenhart R, Kimmig BN, Hover KH, Wowra B, Romahn J, Lorenz WJ, et al. Long-term follow-up for brain metastases treated by percutaneous stereotactic single high-dose irradiation. Cancer 1993;71(4):1353-61.

Engenhart R, Kimmig BN, Hover KH, Wowra B, Sturm V, van Kaick G, et al. Stereotactic single high dose radiation therapy of benign intracranial meningiomas. Int J Radiat Oncol Biol Phys 1990;19(4):1021-6.

Epstein ME, Lindquist C. Cost accounting the Gamma Knife. Stereotact Funct Neurosurg 1993;61 Suppl 1:6-10.

Ertl A, Saringer W, Heimberger K, Kindl P. Quality assurance for the Leksell gamma unit: considering magnetic resonance image-distortion and delineation failure in the targeting of the internal auditory canal. Med Phys 1999;26(2):166-70.

Estrada J, Boronat M, Mielgo M, Magallon R, Millan I, Diez S, et al. The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med 1997;336(3):172-7.

Eustacchio S, Leber K, Trummer M, Unger F, Pendl G. Gamma knife radiosurgery for glomus jugulare tumours. Acta Neurochir (Wien) 1999;141(8):811-8.

Fabrikant JI, Levy RP, Steinberg GK, Phillips MH, Frankel KA, Silverberg GD. Stereotactic charged-particle radiosurgery: clinical results of treatment of 1200 patients with intracranial arteriovenous malformations and pituitary disorders. Clin Neurosurg 1992;38:472-92.

Feuvret L, Germain I, Cornu P, Boisserie G, Noel G, Hardiman C, *et al.* Traitement premier des métastases cérébrales par irradiation en conditions stéréotaxiques. Bull Cancer 1999;86(7-8):666-72.

Fisher AW, Holfelder H. Lokales amyloid in Gehirn. Ein sätfolge von Röntgenbestahlung. Deutsche Zeitung Chirurgie 1930;227:475-83.

Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. Int J Radiat Oncol Biol Phys 1994;28(4):797-802.

Flickinger JC, Kondziolka D, Lunsford LD, Pollock BE, Yamamoto M, Gorman DA, et al. A multi-institutional analysis of complication outcomes after arteriovenous malformation radiosurgery. Int J Radiat Oncol Biol Phys 1999;44(1):67-74.

Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD. Analysis of neurological sequelae from radiosurgery of arteriovenous malformations: how location affects outcome. Int J Radiat Oncol Biol Phys 1998;40(2):273-8.

Flickinger JC, Kondziolka D, Pollock BE, Lunsford LD. Evolution in technique for vestibular schwannoma radiosurgery and effect on outcome. Int J Radiat Oncol Biol Phys 1996;36(2): 275-80.

Foote KD, Friedman WA, Buatti JM, Bova FJ, Meeks SA. Linear accelerator radiosurgery in brain tumor management. Neurosurg Clin N Am 1999;10(2):203-42.

Foote RL, Coffey RJ, Swanson JW, Harner SG, Beatty CW, Kline RW, et al. Stereotactic radiosurgery using the gamma knife for acoustic neuromas. Int J Radiat Oncol Biol Phys 1995;32(4): 1153-60.

Friedman DP, Goldman HW, Flanders AE, Gollomp SM, Curran WJ Jr. Stereotactic radiosurgical pallidotomy and thalamotomy with the gamma knife: MR imaging findings with clinical correlation—preliminary experience. Radiology 1999;212(1):143-50.

Friedman WA, Bova FJ. The University of Florida radiosurgery system. Surg Neurol 1989;32(5): 334-42.

Gaffey CT, Montoya VJ, Lyman JT, Howard J. Restriction of the spread of epileptic discharges in cats by means of Bragg peak, intracranial irradiation. Int J Appl Radiat Isot 1981;32(11):779-84.

Gannett D, Stea B, Lulu B, Adair T, Verdi C, Hamilton A. Stereotactic radiosurgery as an adjunct to surgery and external beam radiotherapy in the treatment of patients with malignant gliomas. Int J Radiat Oncol Biol Phys 1995;33(2):461-8.

Ganz JC, Backlund EO, Thorsen FA. The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies. Stereotact Funct Neurosurg 1993;61 Suppl 1:30-7.

Ganz JC, Mathisen JR, Backlund EO. [Radiosurgery. a different kind of neurosurgery]. Tidsskr Nor Laegeforen 1991;111(25):3076-8.

Goldsmith BJ, Wara WM, Wilson CB, Larson DA. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. J Neurosurg 1994;80(2):195-201.

Grant W 3rd, Woo SY. Clinical and financial issues for intensity-modulated radiation therapy delivery. Semin Radiat Oncol 1999;9(1):99-107.

Grob JJ, Regis J, Laurans R, Delaunay M, Wolkenstein P, Paul K, et al. Radiosurgery without whole brain radiotherapy in melanoma brain metastases. Club de Cancérologie Cutanée. Eur J Cancer 1998;34(8):1187-92.

Guenot M, Wager M, Bataille B, Irani J, Lapierre F. Métastases cérébrales des cancers testiculaires. A propos de deux cas et revue de la littérature. Neurochirurgie 1994;40(2):135-7.

Guo WY, Lindquist C, Karlsson B, Kihlstrom L, Steiner L. Gamma knife surgery of cerebral arteriovenous malformations: serial MR imaging studies after radiosurgery. Int J Radiat Oncol Biol Phys 1993;25(2):315-23.

Hakanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 1981;9(6):638-46.

Hakim R, Alexander E 3rd, Loeffler JS, Shrieve DC, Wen P, Fallon MP, et al. Results of linear accelerator-based radiosurgery for intracranial meningiomas. Neurosurgery 1998;42(3):446-53; discussion 453-4.

Hall WA, Djalilian HR, Sperduto PW, Cho KH, Gerbi BJ, Gibbons JP, et al. Stereotactic radiosurgery for recurrent malignant gliomas. J Clin Oncol 1995;13(7):1642-8.

Hammoud MA, McCutcheon IE, Elsouki R, Schoppa D, Patt YZ. Colorectal carcinoma and brain metastasis: distribution, treatment, and survival. Ann Surg Oncol 1996;3(5):453-63.

Harsh G, Loeffler JS, Thornton A, Smith A, Bussiere M, Chapman PH. Stereotactic proton radiosurgery. Neurosurg Clin N Am 1999;10(2):243-56.

Heikkinen ER, Konnov B, Melnikov L, Yalynych N, Zubkov YuN, Garmashov YuA, et al. Relief of epilepsy by radiosurgery of cerebral arteriovenous malformations. Stereotact Funct Neurosurg 1989;53(3):157-66.

Ishikawa S, Otsuki T, Kaneki M, Jokura H, Yoshimoto T. Dose-related effects of single focal irradiation in the medial temporal lobe structures in rats - magnetic resonance imaging and histological study. Neurol Med Chir (Tokyo) 1999;39(1):1-7.

Ishizuka T, Tomoda Y, Kaseki S, Goto S, Hara T, Kobayashi T. Intracranial metastasis of choriocarcinoma. A clinicopathologic study. Cancer 1983;52(10):1896-903.

Ito K, Kurita H, Sugasawa K, Mizuno M, Sasaki T. Analyses of neuro-otological complications after radiosurgery for acoustic neurinomas. Int J Radiat Oncol Biol Phys 1997;39(5):983-8.

Iwai Y, Yamanaka K, Nakajima H, Yasui T. Stereotactic radiosurgery for cavernous sinus cavernous hemangioma - case report. Neurol Med Chir (Tokyo) 1999;39(4):288-90.

Jackson IM, Norén G. Role of gamma knife therapy in the management of pituitary tumors. Endocrinol Metab Clin North Am 1999;28(1):133-42.

Jacobs P, Bachynsky J. An Alberta standard cost list for health economic evaluations. Edmonton: Institute of Health Economics, 1997.

Jacobs P, Hhanahan M, Roos NP, Farnworth M. Cost list for Manitoba health services. Winnipeg: Manitoba Centre for Health Policy and Evaluation, 1999.

Jenike MA, Rauch SL. Managing the patient with treatment-resistant obsessive compulsive disorder: current strategies. J Clin Psychiatry 1994;55 Suppl:11-7.

Joanes V, Cerda-Nicolas M, Ciudad J, Barcia-Salorio JL. Experimental arterial lesions after narrow-beam gamma irradiation used in stereotactic radiosurgery. Acta Neurochir (Wien) 1998; 140(10):1077-81.

Jokura H, Takahashi K, Kayama T, Yoshimoto T. Gamma knife radiosurgery of a series of only minimally selected metastatic brain tumours. Acta Neurochir Suppl (Wien) 1994;62:77-82.

Joseph J, Adler JR, Cox RS, Hancock SL. Linear accelerator-based stereotaxic radiosurgery for brain metastases: the influence of number of lesions on survival. J Clin Oncol 1996;14(4):1085-92.

Karlsson B, Lax I, Soderman M. Can the probability for obliteration after radiosurgery for arteriovenous malformations be accurately predicted? Int J Radiat Oncol Biol Phys 1999;43(2):313-9.

Karzmark CJ. Advances in linear accelerator design for radiotherapy. Med Phys 1984;11(2):105-28.

Kaylie DM, Horgan MJ, Delashaw JB, McMenomey SO. A meta-analysis comparing outcomes of microsurgery and gamma knife radiosurgery. Laryngoscope 2000;110(11):1850-6.

Kehrli P. Épidémiologie des métastases cérébrales. Neurochirurgie 1999;45(5):357-63.

Kida Y, Kobayashi T, Mori Y. Radiosurgery of angiographically occult vascular malformations. Neurosurg Clin N Am 1999;10(2):291-303.

Kida Y, Kobayashi T, Tanaka T. Radiosurgery of the metastatic brain tumours with gamma-knife. Acta Neurochir Suppl (Wien) 1995;63:89-94.

Kihlstrom L, Guo WY, Karlsson B, Lindquist C, Lindqvist M. Magnetic resonance imaging of obliterated arteriovenous malformations up to 23 years after radiosurgery. J Neurosurg 1997;86(4): 589-93.

Kihlstrom L, Karlsson B. Imaging changes after radiosurgery for vascular malformations, functional targets, and tumors. Neurosurg Clin N Am 1999;10(2):167-80.

Kihlstrom L, Karlsson B, Lindquist C. Gamma Knife surgery for cerebral metastases. Implications for survival based on 16 years experience. Stereotact Funct Neurosurg 1993;61 Suppl 1:45-50.

Kim YS, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for patients with nonsmall cell lung carcinoma metastatic to the brain. Cancer 1997;80(11):2075-83.

Kitchen N. Experimental and clinical studies on the putative therapeutic efficacy of cerebral irradiation (radiotherapy) in epilepsy. Epilepsy Res 1995;20(1):1-10.

Kjellberg RN, Abbe M. Stereotactic Bragg peak proton beam therapy. In: Lunsford LD, editor. Modern stereotactic neurosurgery. Boston: Martinus Nijhoof, 1988, pp. 463-70.

Kobayashi T, Tanaka T, Kida Y. The early effects of gamma knife on 40 cases of acoustic neurinoma. Acta Neurochir Suppl (Wien) 1994;62:93-7.

Kondziolka D, Flickinger JC, Bissonette DJ, Bozik M, Lunsford LD. Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasms. Neurosurgery 1997;41(4):776-83; discussion 783-5.

Kondziolka D, Levy EI, Niranjan A, Flickinger JC, Lunsford LD. Long-term outcomes after meningioma radiosurgery: physician and patient perspectives. J Neurosurg 1999;91(1):44-50.

Kondziolka D, Lunsford LD, Flickinger JC, Kestle JR. Reduction of hemorrhage risk after stereotactic radiosurgery for cavernous malformations. J Neurosurg 1995;83(5):825-31.

Kondziolka D, Lunsford LD, Flickinger JC, Young RF, Vermeulen S, Duma CM, et al. Stereotactic radiosurgery for trigeminal neuralgia: a multiinstitutional study using the gamma unit. J Neurosurg 1996;84(6):940-5.

Kondziolka D, Mori Y, Martinez AJ, McLaughlin MR, Flickinger JC, Lunsford LD. Beneficial effects of the radioprotectant 21-aminosteroid U-74389G in a radiosurgery rat malignant glioma model. Int J Radiat Oncol Biol Phys 1999a;44(1):179-84.

Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for meningiomas. Neurosurg Clin N Am 1999b;10(2):317-25.

Kondziolka D, Perez B, Flickinger JC, Habeck M, Lunsford LD. Gamma knife radiosurgery for trigeminal neuralgia: results and expectations. Arch Neurol 1998;55(12):1524-9.

Königsmaier H, de Pauli-Ferch B, Hackl A, Pendl G. The costs of radiosurgical treatment: comparison between gamma knife and linear accelerator. Acta Neurochir (Wien) 1998;140(11):1101-10; discussion 1110-1.

Kramer S. The hazards of therapeutic irradiation of the central nervous system. Clin Neurosurg 1968; 15:301-18.

Kurita H, Sasaki T, Kawamoto S, Taniguchi M, Terahara A, Tago M, Kirino T. Role of radiosurgery in the management of cavernous sinus meningiomas. Acta Neurol Scand 1997;96(5):297-304.

Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J, et al. Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy. J Neurosurg 1998;88(6):1002-8.

Laws ER Jr, Vance ML. Radiosurgery for pituitary tumors and craniopharyngiomas. Neurosurg Clin N Am 1999;10(2):327-36.

Lax I, Karlsson B. Prediction of complications in gamma knife radiosurgery of arteriovenous malformation. Acta Oncol 1996;35(1):49-55.

Lederman G, Arbit E, Lowry J. Management of acoustic neuroma. N Engl J Med 1999;340(14): 1119-20; discussion 1120-1.

Leksell L. A note on the treatment of acoustic tumours. Acta Chir Scand 1971a;137(8):763-5.

Leksell L. Sterotaxic radiosurgery in trigeminal neuralgia. Acta Chir Scand 1971b;137(4):311-4.

Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 1951;102:316-9.

Levivier M, Wikier D, Goldman S, David P, Metens T, Massager N, et al. Integration of the metabolic data of positron emission tomography in the dosimetry planning of radiosurgery with the gamma knife: early experience with brain tumors. Technical note. J Neurosurg 2000;93 Suppl 3:233-8.

Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Lyman JT, Lawrence JH, et al. Heavy-charged-particle radiosurgery of the pituitary gland: clinical results of 840 patients. Stereotact Funct Neurosurg 1991;57(1-2):22-35.

Lindquist C, Guo WY, Karlsson B, Steiner L. Radiosurgery for venous angiomas. J Neurosurg 1993; 78(4):531-6.

Lindquist C, Kihlstrom L, Hellstrand E. Functional neurosurgery—a future for the gamma knife? Stereotact Funct Neurosurg 1991;57(1-2):72-81.

Linskey ME, Flickinger JC, Lunsford LD. Cranial nerve length predicts the risk of delayed facial and trigeminal neuropathies after acoustic tumor stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 1993;25(2):227-33.

Linskey ME, Lunsford LD, Flickinger JC. Radiosurgery for acoustic neurinomas: early experience. Neurosurgery 1990;26(5):736-44; discussion 744-5.

Linzer D, Ling SM, Villalobos H, Raub W Jr, Wu X, Ting J, et al. Gamma knife radiosurgery for large volume brain tumors: an analysis of acute and chronic toxicity. Stereotact Funct Neurosurg 1998;70 Suppl 1:11-8.

Lippitz BE, Mindus P, Meyerson BA, Kihlstrom L, Lindquist C. Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: relevance of the right hemisphere. Neurosurgery 1999;44(3):452-8; discussion 458-60.

Liscak R, Simonova G, Vymazal J, Janouskova L, Vladyka V. Gamma knife radiosurgery of meningiomas in the cavernous sinus region. Acta Neurochir (Wien) 1999a;141(5):473-80.

Liscak R, Vladyka V, Wowra B, Kemeny A, Forster D, Burzaco JA, et al. Gamma Knife radiosurgery of the glomus jugulare tumour—early multicentre experience. Acta Neurochir (Wien) 1999b;141(11):1141-6.

Loeffler JS, Alexander E 3d. The role of stereotactic radiosurgery in the management of intracranial tumors. Oncology (Huntingt) 1990;4(3):21-31; discussion 32, 37, 41.

Loeffler JS, Alexander E 3d, Shea WM, Wen PY, Fine HA, Kooy HM, et al. Radiosurgery as part of the initial management of patients with malignant gliomas. J Clin Oncol 1992;10(9):1379-85.

Loeffler JS, Barker FG, Chapman PH. Role of radiosurgery in the management of central nervous system metastases. Cancer Chemother Pharmacol 1999;43 Suppl:S11-4.

Loeffler JS, Lindquist C. Radiosurgery for brain tumours. BMJ 1999;319(7206):383.

Lopes AC, Soares KVS. Surgery for obsessive-compulsive disorder (protocol for a Cochrane Review). In: The Cochrane Library Oxford: update software, 1999.

Lunsford LD. Stereotactic radiosurgery of intracranial arteriovenous malformations. In: Wilkins RH, Rengachary SS, editors. Neurosurgery update. New York: McGraw-Hill, 1990, pp. 175-85.

Lunsford LD, Kondziolka D, Flickinger JC. Acoustic neuroma management: Evolution and revolution. In: Kondziolka D, editor. Radiosurgery. Basel: Karger, 1997, pp. 1-7.

Lunsford LD, Kondziolka D, Maitz A, Flickinger JC. Black holes, white dwarfs and supernovas: imaging after radiosurgery. Stereotact Funct Neurosurg 1998;70 Suppl 1:2-10.

Lunsford LD, Witt TC, Kondziolka D, Flickinger JC. Stereotactic radiosurgery of anterior skull base tumors. Clin Neurosurg 1995;42:99-118.

Maguire PD, Clough R, Friedman AH, Halperin EC. Fractionated external-beam radiation therapy for meningiomas of the cavernous sinus. Int J Radiat Oncol Biol Phys 1999;44(1):75-9.

Martens F, Verbeke L, Piessens M, Van Vyve M. Stereotactic radiosurgery of vestibular schwannomas with a linear accelerator. Acta Neurochir Suppl (Wien) 1994;62:88-92.

McCollough WM, Marcus RB Jr, Rhoton AL Jr, Ballinger WE, Million RR. Long-term follow-up of radiotherapy for pituitary adenoma: the absence of late recurrence after greater than or equal to 4500 cGy. Int J Radiat Oncol Biol Phys 1991;21(3):607-14.

McCord MW, Buatti JM, Fennell EM, Mendenhall WM, Marcus RB Jr, Rhoton AL, et al. Radiotherapy for pituitary adenoma: long-term outcome and sequelae. Int J Radiat Oncol Biol Phys 1997;39(2):437-44.

Medicare Services Advisory Committee (MSAC). Gamma knife radiosurgery. Canberra, Australia: MSAC, 2001.

Meeks SL, Bova FJ, Friedman WA, Buatti JM, Mendenhall WM. Linac scalpel radiosurgery at the University of Florida. Med Dosim 1998;23(3):177-85.

Meeks SL, Bova FJ, Kim S, Tome WA, Buatti JM, Friedman WA. Dosimetric characteristics of a double-focused miniature multileaf collimator. Med Phys 1999;26(5):729-33.

Mehta MP. Radiosurgery of malignant brain tumors. In: De Salles A, Lufkin RB, editors. Minimally invasive therapy of the brain. New York: Thieme, 1997, pp. 213-24.

Mehta MP, Rozental JM, Levin AB, Mackie TR, Kubsad SS, Gehring MA, et al. Defining the role of radiosurgery in the management of brain metastases. Int J Radiat Oncol Biol Phys 1992;24(4):619-25.

Mesic JB, Hanks GE, Doggett RL. The value of radiation therapy as an adjuvant to surgery in intracranial meningiomas. Am J Clin Oncol 1986;9(4):337-40.

Miller RC, Foote RL, Coffey RJ, Sargent DJ, Gorman DA, Schomberg PJ, et al. Decrease in cranial nerve complications after radiosurgery for acoustic neuromas: a prospective study of dose and volume. Int J Radiat Oncol Biol Phys 1999;43(2):305-11.

Miyawaki L, Dowd C, Wara W, Goldsmith B, Albright N, Gutin P, et al. Five year results of LINAC radiosurgery for arteriovenous malformations: outcome for large AVMS. Int J Radiat Oncol Biol Phys 1999;44(5):1089-106.

Modan B, Baidatz D, Mart H, Steinitz R, Levin SG. Radiation-induced head and neck tumours. Lancet 1974;1(7852):277-9.

Modell JG, Mountz JM, Curtis GC, Greden JF. Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci 1989;1(1):27-36.

Mori Y, Kondziolka D, Flickinger JC, Logan T, Lunsford LD. Stereotactic radiosurgery for brain metastasis from renal cell carcinoma. Cancer 1998;83(2):344-53.

Morita A, Coffey RJ, Foote RL, Schiff D, Gorman D. Risk of injury to cranial nerves after gamma knife radiosurgery for skull base meningiomas: experience in 88 patients. J Neurosurg 1999; 90(1):42-9.

Motti ED, Losa M, Pieralli S, Zecchinelli A, Longobardi B, Giugni E, et al. Stereotactic radiosurgery of pituitary adenomas. Metabolism 1996;45(8 Suppl 1):111-4.

Muacevic A, Kreth FW, Horstmann GA, Schmid-Elsaesser R, Wowra B, Steiger HJ, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. J Neurosurg 1999;91(1):35-43.

Muthukumar N, Kondziolka D, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for anterior foramen magnum meningiomas. Surg Neurol 1999a;51(3):268-73.

Muthukumar N, Kondziolka D, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for jugular foramen schwannomas. Surg Neurol 1999b;52(2):172-9.

Myers JK, Weissman MM, Tischler GL, Holzer CE 3rd, Leaf PJ, Orvaschel H, et al. Six-month prevalence of psychiatric disorders in three communities 1980 to 1982. Arch Gen Psychiatry 1984;41(10):959-67.

Nataf F, Merienne L, Devaux B, Turak B, Page P, Roux FX. Place de la radiochirurgie dans le traitement des adénomes hypophysaires. Neurochirurgie 1998;44(5):339-43.

Nedzi LA, Kooy H, Alexander E 3d, Gelman RS, Loeffler JS. Variables associated with the development of complications from radiosurgery of intracranial tumors. Int J Radiat Oncol Biol Phys 1991;21(3):591-9.

Niemela M, Lim YJ, Soderman M, Jaaskelainen J, Lindquist C. Gamma knife radiosurgery in 11 hemangioblastomas. J Neurosurg 1996;85(4):591-6.

Nizin PS. On absorbed dose in narrow 60Co gamma-ray beams and dosimetry of the gamma knife. Med Phys 1998;25(12):2347-51.

Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys 1994;29(4):711-7.

Norén G. Gamma Knife radiosurgery for acoustic neurinomas. In: Gildenberg PL, Tasker RR, editors. Textbook of stereotactic and functional neurosurgery. New York: McGraw-Hill, 1998, pp. 835-44.

Norén G, Greitz D, Hirsch A, Lax I. Gamma knife surgery in acoustic tumours. Acta Neurochir Suppl (Wien) 1993;58:104-7.

Nugent JL, Bunn PA Jr, Matthews MJ, Ihde DC, Cohen MH, Gazdar A, et al. CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. Cancer 1979;44(5):1885-93.

Ogunrinde OK, Lunsford DL, Kondziolka DS, Bissonette DJ, Flickinger JC. Cranial nerve preservation after stereotactic radiosurgery of intracanalicular acoustic tumors. Stereotact Funct Neurosurg 1995;64 Suppl 1:87-97.

Ohye C, Shibazaki T, Hirato M, Inoue H, Andou Y. Gamma thalamotomy for parkinsonian and other kinds of tremor. Stereotact Funct Neurosurg 1996;66 Suppl 1:333-42.

Oregon Health Resources Commission. Technology assessment and health resources plan: stereotactic radiosurgery. Oregon Health Plan Policy and Research, Heath Resources Commission, 1997.

Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322(8):494-500.

Patronas NJ, Di Chiro G, Brooks RA, DeLaPaz RL, Kornblith PL, Smith BH, et al. Work in progress: [18F] fluorodeoxyglucose and positron emission tomography in the evaluation of radiation necrosis of the brain. Radiology 1982;144(4):885-9.

Paulsen RD, Steinberg GK, Norbash AM, Marcellus ML, Lopez JR, Marks MP. Embolization of rolandic cortex arteriovenous malformations. Neurosurgery 1999a;44(3):479-84; discussion 484-6.

Paulsen RD, Steinberg GK, Norbash AM, Marcellus ML, Marks MP. Embolization of basal ganglia and thalamic arteriovenous malformations. Neurosurgery 1999b;44(5):991-6; discussion 996-7.

Pendl G, Schrottner O, Eustacchio S, Feichtinger K, Ganz J. Stereotactic radiosurgery of skull base meningiomas. Minim Invasive Neurosurg 1997;40(3):87-90.

Pennybacker J, Russell DS. Necrosis of the brain due the radiation therapy. J Neurol Neurosurg Psychiatry 1948;2:183-98.

Petty AM, Kun LE, Meyer GA. Radiation therapy for incompletely resected meningiomas. J Neurosurg 1985;62(4):502-7.

Pistenma DA, Goffinet DR, Bagshaw MA, Hanbery JW, Eltringham JR. Treatment of acromegaly with megavoltage radiation therapy. Int J Radiat Oncol Biol Phys 1976;1(9-10):885-93.

Podgorsak EB, Olivier A, Pla M, Lefebvre PY, Hazel J. Dynamic stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 1988;14(1):115-26.

Pollock BE, Kondziolka D, Flickinger JC, Maitz A, Lunsford LD. Preservation of cranial nerve function after radiosurgery for nonacoustic schwannomas. Neurosurgery 1993;33(4):597-601.

Prasad D. Gamma Knife Surgery, microsurgery, microsurgery, and modified linear accelerator radiosurgery. A review of published results. Charlottesville: Department of Neurosurgery, University of Virginia, 1999.

Québec. Ministère de la Santé et des Services Sociaux. CD Explorateur DRG Québec 1998-99 [CD-ROM]. Québec: MSSS, 2000.

Radanowicz-Harttmann V, Bachli H, Gratzl O. Late complication of radiosurgery of AVMs with the gamma knife: a case report. Acta Neurochir (Wien) 1998;140(2):194-5.

Rähn T, Thorén M, Werner S. Stereotactic surgery in pituitary adenomas. In: Etal GF, editor. Pituitary adenomas: New Trends in basic and clinical research. New York: Excerpta Medica, 1991, pp. 303-12.

Rand RW, Jacques DB, Melbye RW, Copcutt BG, Fisher MR, Levenick MN. Gamma Knife thalamotomy and pallidotomy in patients with movement disorders: preliminary results. Stereotact Funct Neurosurg 1993;61 Suppl 1:65-92.

Rand RW, Jacques DB, Melbye RW, Copcutt BG, Irwin L. Gamma knife radiosurgery for metastatic brain tumors. Acta Neurochir Suppl (Wien) 1995;63:85-8.

Rasmussen SA, Eisen JL. The epidemiology and differential diagnosis of obsessive compulsive disorder. J Clin Psychiatry 1992;53 Suppl:4-10.

Regis J, Bartolomei F, Metellus P, Rey M, Genton P, Dravet C, et al. Radiosurgery for trigeminal neuralgia and epilepsy. Neurosurg Clin N Am 1999a;10(2):359-77.

Regis J, Bartolomei F, Rey M, Genton P, Dravet C, Semah F, et al. Gamma knife surgery for mesial temporal lobe epilepsy. Epilepsia 1999b;40(11):1551-6.

Regis J, Kerkerian-Legoff L, Rey M, Vial M, Porcheron D, Nieoullon A, et al. First biochemical evidence of differential functional effects following Gamma Knife surgery. Stereotact Funct Neurosurg 1996;66 Suppl 1:29-38.

Regis J, Manera L, Dufour H, Porcheron D, Sedan R, Peragut JC. Effect of the Gamma Knife on trigeminal neuralgia. Stereotact Funct Neurosurg 1995a;64 Suppl 1:182-92.

Regis J, Peragut JC, Rey M, Samson Y, Levrier O, Porcheron D, et al. First selective amygdalohippocampal radiosurgery for 'mesial temporal lobe epilepsy'. Stereotact Funct Neurosurg 1995b;64 Suppl 1:193-201.

Rocher FP, Sentenac I, Berger C, Marquis I, Romestaing P, Gerard JP. Stereotactic radiosurgery: the Lyon experience. Acta Neurochir Suppl (Wien) 1995;63:109-14.

Ross IB, Tator CH. Stereotactic radiosurgery for acoustic neuroma: a Canadian perspective. Can J Neurol Sci 1998;25(4):310-4.

Rossi GF, Scerrati M, Roselli R. Epileptogenic cerebral low-grade tumors: effect of interstitial stereotactic irradiation on seizures. Appl Neurophysiol 1985;48(1-6):127-32.

Rougier A, Dartigues JF, Commenges D, Claverie B, Loiseau P, Cohadon F. A longitudinal assessment of seizure outcome and overall benefit from 100 cortectomies for epilepsy. J Neurol Neurosurg Psychiatry 1992;55(9):762-7.

Rutigliano MJ, Lunsford LD, Kondziolka D, Strauss MJ, Khanna V, Green M. The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. Neurosurgery 1995;37(3):445-53; discussion 453-5.

Salcman M. Survival in glioblastoma: historical perspective. Neurosurgery 1980;7(5):435-9.

Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with an emphasis on complications and how to avoid them. Neurosurgery 1997a;40(1):11-21; discussion 21-3.

Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): hearing function in 1000 tumor resections. Neurosurgery 1997b;40(2):248-60; discussion 260-2.

Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): the facial nerve—preservation and restitution of function. Neurosurgery 1997c;40(4):684-94; discussion 694-5.

Sarkaria JN, Mehta MP, Loeffler JS, Buatti JM, Chappell RJ, Levin AB, et al. Radiosurgery in the initial management of malignant gliomas: survival comparison with the RTOG recursive partitioning analysis. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1995; 32(4):931-41.

Sasson Y, Zohar J, Chopra M, Lustig M, Iancu I, Hendler T. Epidemiology of obsessive-compulsive disorder: a world view. J Clin Psychiatry 1997;58 Suppl 12:7-10.

Schneider WL, Hailey D. Stereotactic radiosurgery: options for Albertans. Edmonton: Alberta Heritage Foundation for Medical Research, Alberta's Health Technology Program, 1998.

Scrivani SJ, Keith DA, Mathews ES, Kaban LB. Percutaneous stereotactic differential radiofrequency thermal rhizotomy for the treatment of trigeminal neuralgia. J Oral Maxillofac Surg 1999;57(2):104-11; discussion 111-2.

Shafron DH, Friedman WA, Buatti JM, Bova FJ, Mendenhall WM. Linac radiosurgery for benign meningiomas. Int J Radiat Oncol Biol Phys 1999;43(2):321-7.

Shaw E, Scott C, Souhami L, Dinapoli R, Bahary JP, Kline R, et al. Radiosurgery for the treatment of previously irradiated recurrent primary brain tumors and brain metastases: initial report of radiation therapy oncology group protocol (90-05). Int J Radiat Oncol Biol Phys 1996;34(3): 647-54.

Sheline GE, Tyrell B. Pituitary adenomas. In: Black PM, Zervas NT, Ridgway EC, et al., editors. Progress in Endocrine Research and Therapy. Vol. 1. New York: Raven Press, pp. 1-35.

Shiau CY, Sneed PK, Shu HK, Lamborn KR, McDermott MW, Chang S, et al. Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. Int J Radiat Oncol Biol Phys 1997;37(2):375-83.

Shirato H, Sakamoto T, Sawamura Y, Kagei K, Isu T, Kato T, et al. Comparison between observation policy and fractionated stereotactic radiotherapy (SRT) as an initial management for vestibular schwannoma. Int J Radiat Oncol Biol Phys 1999;44(3):545-50.

Solan MJ, Kramer S. The role of radiation therapy in the management of intracranial meningiomas. Int J Radiat Oncol Biol Phys 1985;11(4):675-7.

Somigliana A, Cattaneo GM, Fiorino C, Borelli S, del Vecchio A, Zonca G, et al. Dosimetry of Gamma Knife and linac-based radiosurgery using radiochromic and diode detectors. Phys Med Biol 1999;44(4):887-97.

Spencer SS. Long-term outcome after epilepsy surgery. Epilepsia 1996;37(9):807-13.

Sperling MR, Saykin AJ, Roberts FD, French JA, O'Connor MJ. Occupational outcome after temporal lobectomy for refractory epilepsy. Neurology 1995;45(5):970-7.

Stafford SL, Pollock BE, Foote RL, Gorman DA, Nelson DF, Schomberg PJ. Stereotactic radiosurgery for recurrent ependymoma. Cancer 2000;88(4):870-5.

Steiner L, Lindquist C. Radiosurgery in cerebral arteriovenous malformation. In: Tasker RR, editor. Neurosurgery: state of the arts reviews. Vol. 2. Philadelphia: Hanley & Belfus, 1987, pp. 329-35.

Steiner L, Prasad D, Lindquist C, Steiner M. Clinical aspects of gamma knife stereotactic radiosurgery. In: Gildenberg P, Tasker R, editors. Textbook of stereotactic and functional radiosurgery. New York: McGraw Hill, 1997, Section 10.

Stern RL. Peripheral dose from a linear accelerator equipped with multileaf collimation. Med Phys 1999;26(4):559-63.

Sturm V, Kober B, Hover KH, Schlegel W, Boesecke R, Pastyr O, et al. Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. Int J Radiat Oncol Biol Phys 1987;13(2):279-82.

Subach BR, Lunsford LD, Kondziolka D, Maitz AH, Flickinger JC. Management of petroclival meningiomas by stereotactic radiosurgery. Neurosurgery 1998;42(3):437-43; discussion 443-5.

Takacs I, Hamilton AJ. Extracranial stereotactic radiosurgery: applications for the spine and beyond. Neurosurg Clin N Am 1999;10(2):257-70.

Taylor BW Jr, Marcus RB Jr, Friedman WA, Ballinger WE Jr, Million RR. The meningioma controversy: postoperative radiation therapy. Int J Radiat Oncol Biol Phys 1988;15(2):299-304.

Thoren M, Rahn T, Guo WY, Werner S. Stereotactic radiosurgery with the cobalt-60 gamma unit in the treatment of growth hormone-producing pituitary tumors. Neurosurgery 1991;29(5):663-8.

Trivedi MH. Functional neuroanatomy of obsessive-compulsive disorder. J Clin Psychiatry 1996;57 Suppl 8:26-35; discussion 36.

Tsai JS, Buck BA, Svensson GK, Alexander E 3rd, Cheng CW, Mannarino EG, *et al*. Quality assurance in stereotactic radiosurgery using a standard linear accelerator. Int J Radiat Oncol Biol Phys 1991;21(3):737-48.

Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ. Role of radiation therapy in clinical hormonally-active pituitary adenomas. Radiother Oncol 1996;41(1):45-53.

Tsuruda JS, Kortman KE, Bradley WG, Wheeler DC, Van Dalsem W, Bradley TP. Radiation effects on cerebral white matter: MR evaluation. AJR Am J Roentgenol 1987;149(1):165-71.

Valentino V. The results of radiosurgical management of 139 single cerebral metastases. Acta Neurochir Suppl (Wien) 1995;63:95-100.

Valentino V, Raimondi AJ. Tumour response and morphological changes of acoustic neurinomas after radiosurgery. Acta Neurochir (Wien) 1995;133(3-4):157-63.

Valentino V, Schinaia G, Raimondi AJ. The results of radiosurgical management of 72 middle fossa meningiomas. Acta Neurochir (Wien) 1993;122(1-2):60-70.

Vecht CJ, Haaxma-Reiche H, Noordijk, EM Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 1993;33(6):583-90.

Voges J, Sturm V, Deuss U, Traud C, Treuer H, Schlegel W, et al. LINAC-radiosurgery (LINAC-RS) in pituitary adenomas: preliminary results. Acta Neurochir Suppl (Wien) 1996;65:41-3.

Voges J, Treuer H, Erdmann J, Schlegel W, Pastyr O, Muller RP, et al. Linac radiosurgery in brain metastases. Acta Neurochir Suppl (Wien) 1994;62:72-6.

Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. Int J Radiat Oncol Biol Phys 1989; 16(6):1405-9.

Wallner KE, Sheline GE, Pitts LH, Wara WM, Davis RL, Boldrey EB. Efficacy of irradiation for incompletely excised acoustic neurilemomas. J Neurosurg 1987;67(6):858-63.

Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Lee CK, et al. The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. J Clin Psychiatry 1994;55 Suppl:5-10.

Werner-Wasik M, Rudoler S, Preston PE, Hauck WW, Downes BM, Leeper D, et al. Immediate side effects of stereotactic radiotherapy and radiosurgery. Int J Radiat Oncol Biol Phys 1999;43(2):299-304.

Whang CJ, Kim CJ. Short-term follow-up of stereotactic Gamma Knife radiosurgery in epilepsy. Stereotact Funct Neurosurg 1995;64 Suppl 1:202-8.

Wingkun EC, Awad IA, Luders H, Awad CA. Natural history of recurrent seizures after resective surgery for epilepsy. Epilepsia 1991;32(6):851-6.

Wronski M, Arbit E, McCormick B, Wronski M. Surgical treatment of 70 patients with brain metastases from breast carcinoma. Cancer 1997;80(9):1746-54.

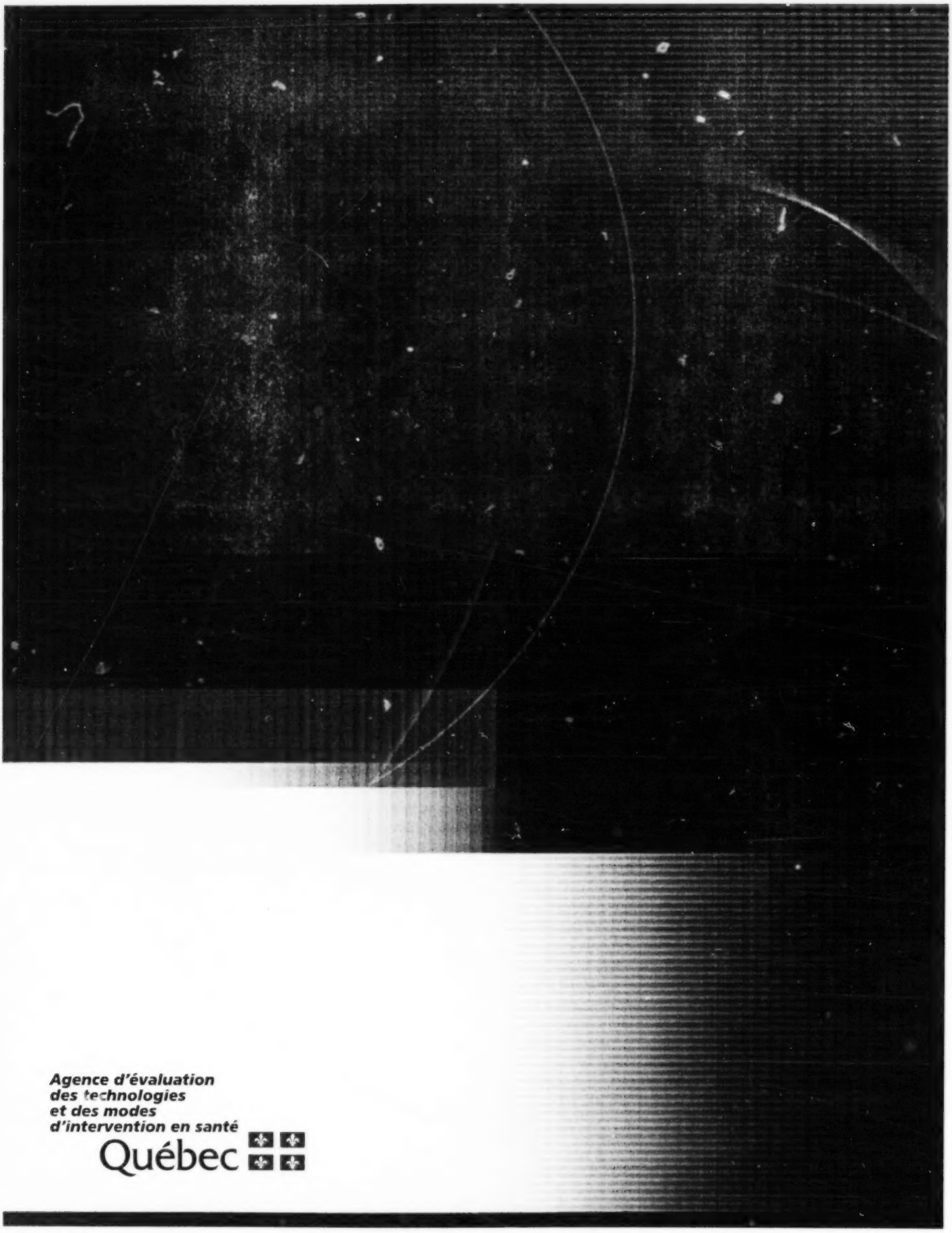
Yamamoto M, Jimbo M, Ide M, Lindquist C, Steiner L. Gamma Knife radiosurgery in cerebral arteriovenous malformations: postobliteration nidus changes observed on neurodiagnostic imaging. Stereotact Funct Neurosurg 1995;64 Suppl 1:126-33.

Young C, Summerfield R, Schwartz M, O'Brien P, Ramani R. Radiosurgery for arteriovenous malformations: the University of Toronto experience. Can J Neurol Sci 1997;24(2):99-105.

Young RF, Jacques DB, Duma C, Rand RW, Henderson J, Vermeulen SS, *et al*. Gamma knife radiosurgery for treatment of multiple brain metastases. In: Kondziolka D, editor. Radiosurgery. Vol. 1. Basel: Karger, 1995, pp. 92-101.

Young RF, Shumway-Cook A, Vermeulen SS, Grimm P, Blasko J, Posewitz A, *et al*. Gamma knife radiosurgery as a lesioning technique in movement disorder surgery. J Neurosurg 1998a;89(2): 183-93.

Young RF, Vermulen S, Posewitz A. Gamma knife radiosurgery for the treatment of trigeminal neuralgia. Stereotact Funct Neurosurg 1998b;70 Suppl 1:192-9.



Agence d'évaluation des technologies et des modes d'intervention en santé

Québec